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BRITISH MEDICAL JOURNAL

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 7 1952

ALLERGY AND A.C.T.H.*

BY

G. W. PICKERING, M.B., M.D.Ghent, F.R.C.P.

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Allergy implies a response of certain tissues of the body to quantities of a specific chemical substance to which in the majority of people there is no response. It is of two broad types. In the first the response to the substance is immediate—that is to say, is timed in seconds or minutes—and the serum of the patient contains a substance by virtue of which reactivity to the specific antigen can be transferred temporarily to a normal person either locally, by subcutaneous injection of serum, or generally, by blood transfusion. This type of allergy includes many cases of hay-fever, urticaria, and non-infective bronchial asthma.

In the second type the response is delayed—that is to say, it is manifest after several hours and is maximal one or two days after exposure; sensitivity to the agent cannot be passively transferred by serum, but can be transferred by certain cells from the sensitized subject. This type includes bacterial allergy, of which the tuberculin reaction is the classical example, and the skin response to certain irritants, like poison ivy, dinitrochlorbenzene, and picryl chloride. Clinically, contact dermatitis is probably the commonest simple example of the delayed type. Cooke (1947) includes infective asthma in this category. Finally, there is some evidence that altered tissue reactivity to certain specific antigens is concerned in some diseases, such as acute nephritis, rheumatic fever, polyarteritis nodosa, and lupus erythematosus, but the evidence concerning the role of allergy in these diseases in man is dangerously thin, and I shall omit them from consideration, as they are more likely to lead us astray than to provide any firm conclusions.

Adrenal Cortical Secretions

A.C.T.H. is the adrenocorticotrophic hormone of the anterior pituitary gland. As ordinarily prepared it is a protein, but Morris and Morris (1950), Astwood (1951), and Li (1951) have obtained all the activity in the form of a peptide, and recent work from F. G. Young's laboratory at Cambridge (Dixon *et al.*, 1951a, 1951b) suggests that the hormone is in fact a peptide which is ordinarily rather loosely attached to protein. It would seem probable that the structure of A.C.T.H. will soon be established and its synthesis is at least possible. It acts exclusively on the cortex of the adrenal gland, causing the discharge of certain steroids into the adrenal vein. The discharge of the steroids is roughly proportional to the amount of A.C.T.H. present in the blood perfusing the gland and virtually ceases in the absence of A.C.T.H.

No fewer than 28 steroids have been isolated from the adrenal gland, and much of the gland's activity, particularly in regard to the control of electrolytes, remains in the "amorphous fraction," the chemical nature of which has not yet been established (Kendall, 1951). Pincus *et al.* (1951) and Bush (1951) have shown that the proportion of different steroids discharged from the perfused adrenal is relatively constant for a given individual regardless of whether the gland is discharging much or little, and that the relative proportions of the individual steroids vary much from one species to another. In the ox, the chief steroids are 17-hydroxycorticosterone (compound F) and corticosterone. Cortisone (compound E) and 11-desoxycorticosterone (D.C.A.) are very minor components.

Thus the control of the adrenal cortical secretions seems to reside in the pituitary. What regulates the secretion of A.C.T.H. is still uncertain. Sayers (1951) believes that ordinarily the level of circulating adrenal steroids is the effective stimulus, and that their removal by active tissues increases the output of A.C.T.H. There is much evidence that the discharge of adrenal corticoids is increased in pregnancy, in injuries, after operations, and by the injection of adrenaline—in fact, in a variety of circumstances that are often collectively and loosely referred to as stress.

So far as we know at present, the only two steroids which are active in suppressing allergic phenomena are cortisone, about which much is known, and 17-hydroxycorticosterone (compound F), about which we know little. If the human adrenal behaves like that of the ox, compound F is probably the effective agent when A.C.T.H. is administered.

The fact that in acute experiments many of the diseases affected by A.C.T.H. are similarly affected by cortisone, and vice versa, suggests that compounds E and F alone of the adrenal steroids are active in this way, a conclusion supported by all clinical trials of the individual steroids thus far conducted. Prolonged therapy with cortisone is complicated by effects on other glands, such as the thyroid, which becomes less active, and by atrophy of the adrenals, which do not respond fully to A.C.T.H. until three weeks after prolonged intramuscular cortisone therapy has ceased (Sprague *et al.*, 1951). Prolonged therapy with A.C.T.H. is complicated by a falling away in its effectiveness, a phenomenon that is as yet imperfectly understood.

*An address to the British Association of Allergists, given in London on February 2, 1952.

Effect of A.C.T.H. and Cortisone on Allergic Diseases

Here I have no first-hand experience to relate, as our own supplies have been used almost entirely in polyarteritis nodosa and disseminated lupus. Recent numbers of publications devoted to allergy have devoted nearly half their space to the effects of A.C.T.H. and cortisone on allergic diseases. It might be thought that by now the clinical effects of the drugs would be known with certainty. That, however, is not the case, partly because many of the cases on which the drugs have been used have been imperfectly investigated, but chiefly because most of the trials have been made without proper controls.

In hay-fever most authors have described improvement, others not, but in the carefully controlled experiments of Carryer, Koelsche, *et al.* (1950) symptoms seemed to be relieved during cortisone therapy, but not completely suppressed. Feinberg *et al.* (1951) have observed no diminution in the sensitivity of the nose or eye to the specific antigen applied locally during A.C.T.H. therapy. Rose *et al.* (1951) found A.C.T.H. ineffective in six out of eight cases of urticaria; Cooke *et al.* (1951) treated five cases of chronic urticaria successfully.

In asthma, A.C.T.H. and cortisone have very generally been reported to have quite dramatically beneficial results. Rose *et al.* (1951) divided their cases into intrinsic (or infective) and extrinsic (or non-infective). In 23 intrinsic cases A.C.T.H. produced a complete remission in two to five days, lasting three to five weeks. Cortisone acted similarly, but rather more slowly. In 19 extrinsic or non-infective cases they found that remission might not occur even with 200 mg. of A.C.T.H. daily for 12 days or with smaller doses of A.C.T.H. and cortisone for one month, and that when remissions did occur they were consistent with the spontaneous remissions natural to the disease, particularly with removal of the patient from his or her home environment. Although no other workers have stressed this difference between infective and non-infective asthma, there are no published experiences that are quite inconsistent with this view. Thus the dramatic effects have been obtained mainly in the infective type (see Cooke *et al.*, 1951). Grob *et al.* (1951) tested three of their patients with ragweed aerosols, recording the diminution in maximum breathing capacity after exposure. Although they thought that A.C.T.H. diminished the response, plotting of dose and response shows no significant relationship between the two.

In dermatitis similar to that attributed to sensitivity of the delayed type, Cooke *et al.* (1951) have reported relief on the third or fourth day of A.C.T.H. therapy. More striking is the case of atropine sensitivity described by Bordley *et al.* (1949) in which during A.C.T.H. therapy no response was obtained to a hitherto strongly effective dose of atropine.

While, therefore, the position is by no mean clear-cut, it would seem that the effects of A.C.T.H. and cortisone are more consistent and striking in the delayed than in the immediate type of allergic response.

Before leaving therapeutics it is proper to add that A.C.T.H. and cortisone are now known to suppress the more obvious lesions in a number of diseases during the period of their administration. Rheumatoid arthritis, polyarteritis nodosa, beryllium granulomatosis, probably rheumatic fever and disseminated lupus, and a variety of acute and chronic inflammatory diseases of the eye appear to subside during administration of these substances but tend to relapse once treatment is withdrawn.

It is clear, therefore, that these substances have important therapeutic potentialities in diseases for which no other effective treatment is known and of which the causation is understood either imperfectly or not at all. Add to that the consideration that these substances are natural products of the body, and that of all the closely related and highly complex molecular structures so far investigated only two, Kendall's compounds E and F, appear to possess this peculiar action, and you have a situation so pregnant with possibilities that a number of laboratories all over the world have set out to explore it. Two years ago, with the generous assistance of the Nuffield Foundation, my department was enabled to begin work in this field. The work was begun by Dr R. R. H. Lovell and myself and continued by Dr. Lovell, Dr. B. Hudson, and Dr. H. Goodman, and I would like to thank them for allowing me to quote work which is as yet unpublished.

Experimental Inflammations in Man

Since we were ultimately interested in the mechanism of disease processes in man, we have done all our work on man, using doses of A.C.T.H. and cortisone that are therapeutically effective in the diseases mentioned—namely, doses of the order of 100–160 mg. a day of A.C.T.H. and 200 mg. a day of cortisone.

Observations have been made on patients suffering from rheumatoid arthritis and ocular diseases, in which the skin appeared healthy. Our object was to discover which, if any, of the processes concerned under the broad heading of inflammation are affected by A.C.T.H. or cortisone.

We began by making a rather broad survey of responses, including those to histamine and morphine pricked into the skin, the response to pollen and to intracutaneous injections of silver nitrate, manganese butyrate, tuberculin, trichophytin, the Dick and Schick reactions, and the skin response to dinitrochlorbenzene in subjects previously sensitized by a single drop of the substance on the skin. We chose a dose of the test substance which gave a suitable response, and we measured the sizes of the responses elicited by this dose several times before, during, and after treatment with A.C.T.H. or cortisone. The responses to histamine and morphine showed little variation from day to day and were unaffected by A.C.T.H. and cortisone. To test the sensitivity to pollen we used the Prausnitz–Küstner reaction and again obtained fairly constant responses unchanged by A.C.T.H. and cortisone.

The response to silver nitrate was rather variable, and we were unable to say whether it was altered, although we did notice on occasion that cessation of treatment was followed in two or three days by a flare-up of lesions laid down several days earlier during A.C.T.H. or cortisone therapy. The tuberculin and trichophytin responses were likewise variable, and though they showed some tendency to be depressed during the administration of A.C.T.H. and cortisone, and to flare up after its withdrawal, we were unable to convince ourselves of any definite effect. Dinitrochlorbenzene sensitized two patients on whom we made extensive observations. In one, repeated testing of the skin before and during cortisone therapy led to such an enhancement of sensitivity, to such intense responses with reactivation of sites previously tested, and to such intense eosinophilia that we feared an exfoliative dermatitis and desisted. In the other, using serial dilutions, there was evidence of diminished sensitivity during cortisone therapy, with flaring of the sites on withdrawing therapy.

Results of First Year's Work

Our first year's work had left us in a position of some uncertainty, corresponding to the experiences of others in this field published up to that time and since, some recording a suppression of this and that, others none. It was clear that the effect for which we were looking was not gross enough to be detected by such methods, and that we must use methods giving results capable of statistical treatment. Dr. Lovell, Dr. Hudson, and Dr. Goodman therefore investigated the responses to serial dilution of the test agents to see to what extent the size of the response was a linear function of the logarithm of the dose, as described by Squire (1950) for the histamine reaction and the skin reaction to horse-dandruff protein in man, and for the tuberculin reaction in the experimental animal, as described by Wadley (1949) and by Long and Miles (1950). Using both diameter of erythema and of induration, this relationship was found to hold for the response to P.P.D. and to

intracutaneous injections of manganese butyrate. By repeating these dose-response curves three or four times in the fortnight before, the fortnight during, and the fortnight after treatment with A.C.T.H. and cortisone, results have been obtained which can be treated statistically and which have already yielded the following information:

(1) *Reactions to Histamine and Morphine.*—In two cases the sizes of the responses were not altered by cortisone.

(2) *Pollen sensitivity* studied in one case was not altered by cortisone. These results, taken with our earlier ones, which consistently gave a similar answer, convince us that cortisone and A.C.T.H. have no significant effect on the triple response, whether provoked by histamine itself or by mechanisms that probably act by the release of histamine.

(3) The tuberculin response has been studied in six cases that have received cortisone and four that have received A.C.T.H. The responses have been reduced in all cases.

(4) *Manganese butyrate* has been studied in seven cases receiving cortisone and three receiving A.C.T.H. The responses have been reduced in most cases, though less extensively and less constantly than those to tuberculin.

(5) *Sensitivity to Atropine.*—Two patients who had become sensitive to atropine owing to prolonged conjunctival instillation were tested by patch tests with ointment, using the lowest dilution which consistently gave erythema with perifollicular swelling. The skin responses to such dilutions were suppressed during cortisone treatment, as were the conjunctival and palpebral redness and swelling to the eye drops.

Mechanisms in Inflammation

As a result of these observations we feel that the nature of the effect of cortisone and of related steroids on the inflammatory response is beginning to take shape. And, since the reactions which are referred to as allergy may be best seen against the general background of the tissue responses to injury, I shall attempt to sketch this general picture.

Immediate Responses

Lewis (1927) was the first to study in detail the responses of the skin to injury. He showed that many injurious agents produced a common response with three components —a local red reaction due to dilatation of minute vessels, a wheal due to their increased permeability, and a surrounding flare due to arteriolar dilatation. This triple response Lewis showed was identical with the response to histamine, and he suggested that all injurious agents giving this type of response acted by causing the release of histamine, or something very like it, from the injured cells. Proof that morphine does in fact cause the release of histamine from the cells of the skin has recently been provided by Feldberg and Paton (1951). Amongst the reactions shown to cause the release of histamine or similar substance was that to the introduction of pollen, fish, and other extracts into the skin of sensitive subjects (Lewis and Grant, 1926; Hare, 1926). It has since been shown that these responses are diminished by histamine antagonists. Thus allergic urticaria would seem to be due to the release of histamine by the skin cells stimulated by the reaction with antigen and antibody (reagin). The phenomena of hay-fever may be similarly interpreted as the conjunctival and nasal mucosal responses to antigens causing the local release of histamine.

Asthma has also been so interpreted, but there is a good deal of evidence that histamine does not play a major part. Thus it is said that antihistamines are relatively ineffective in asthma. In a beautiful short paper Schiller and Lowell (1947) pointed out that much could be learned of asthma by measuring vital capacities before and during inhalation of solutions suspended in fine droplets in the inhaled air. They showed that three asthmatics each responded with a pronounced fall in vital capacity to inhalation of pollen extracts, and that these falls could be prevented by aminophylline or adrenaline, but not by pyribenzamine or atropine. Histamine aerosols gave similar reductions in vital capacity that were prevented by pyribenzamine but not by atropine, while the responses to acetyl-β-methylcholine were preventable by atropine but not by pyribenzamine. Again, there is evidence that the phenomena of anaphylactic shock are in part due to the release of histamine from various cells of the body through the reaction of antigen with antibody, though there is also evidence for the release of other substances in addition to histamine (Feldberg, 1941; Rose, 1947).

In these reactions, time relations and pharmacological assay alike suggest that the histamine is released from the cell and is not manufactured in response to the injurious agent. If in a pollen-sensitive subject solutions of histamine, morphine, and pollen are placed on the skin, and pricked through successively within a period of five seconds, the wheals and flares develop nearly simultaneously with morphine and histamine, beginning in about 30 seconds. As Hare (1926) had found, the response to a protein antigen begins about a minute later. It is clear that the latent period between the contact of morphine or of antigen with the cell and the appearance of histamine outside it is very short.

Other substances, too—notably potassium, acetylcholine, and adrenaline—can be released very quickly from cells. All these substances exist preformed in the cell and presumably are present very near the cell membrane. Perhaps with the exception of potassium they are present in pharmacologically inert form in a lipo-protein film, and are released by substances altering the stability of this film. Feldberg and Kellaway (1938) have brought evidence to show that one of the ways in which histamine can be released is by the action of a lecithinase on lecithin, producing lysolecithin, which is haemolytic and causes release of histamine from most cells, and of adrenaline from the cells of the adrenal (Feldberg, 1940).

This type of cellular response, in which there is a very quick release of histamine and probably of other pharmacologically active substances, appears to be unaffected, or only slightly affected, by A.C.T.H. and cortisone. As has been shown here, cortisone does not interfere with the action of histamine on the human skin blood vessels or its release by morphine or its release by pollen antigen in sensitive subjects. Whether it has any action on allergic urticaria, hay-fever, or extrinsic non-infective asthma is at present doubtful, though it seems clear that its effects in these conditions are less striking than in infective asthma or dermatitis of the contact type—though these therapeutic statements may require revision with further experience. In animals it does not affect the release of histamine from sheep's red cells treated with the plasma of rabbits previously sensitized to sheep's red cells (Carryer and Code, 1950). Cortisone and A.C.T.H. do not reduce the general or local anaphylactic response to the antigen in guinea-pigs previously sensitized to it (Landau *et al.*, 1951).

Delayed Responses

Certain tissue responses to injury are delayed, and among them are some of those classed as allergic, particularly those of contact dermatitis and those of bacterial allergy. Lewis (1927) thought that some delayed responses such as that to ultra-violet light were due to the delayed release of the H substance concerned in immediate responses. But these responses in general contain a new element wholly lacking from the histamine response—namely, the accumulation of cells, polymorphonuclear leucocytes, lymphocytes, macrophages, and others. It seems extremely probable that these cells enter the tissues from the blood vessels or migrate from neighbouring tissues or result from the mitosis of existing cells, because of the local accumulation of chemical substances produced by tissue injury. The cellular reactions are different with different injuries: silver nitrate produces almost entirely a polymorphonuclear response, tuberculin and manganese butyrate produce mixed responses, with mononuclears predominant from 48 hours on. These differences suggest that more than one substance is concerned in the response.

Menkin (1940) showed that the cell-free fluid from inflammatory exudates would attract polymorphonuclear leucocytes and increase capillary permeability, effects which he attributed to a single substance—leucotaxin. Subsequent work by Duthie and Chain (1939), Cullumbine and Rydon (1946), and Spector (1951) suggests that leucotaxin is not a single entity, but a whole series of polypeptides, produced by proteolysis, that have the power to increase capillary permeability and to attract leucocytes. Peters (1945), during a search for the biochemical basis of thermal burns, showed the presence in skin of a protease active at *p*H 7 and inhibited by a factor present in plasma. He showed that this protease was released from the skin after burning, and attributed the separation of the epidermal cells to its action. Cullumbine and Rydon showed that this skin protease produced leucotaxin. They also showed that there was a very large accumulation of leucotaxin in skin several hours after applying lewisite to it. It would therefore seem that one type of delayed response to injury is due to the release of a tissue protease which, acting on tissue and plasma protein, liberates polypeptides, collectively known as leucotaxin, that elicit the vascular and cellular response. The delay in this form of response would be partly accounted for by the time taken for the protease to digest the proteins.

It is extremely probable that other mechanisms are also involved in the delayed type of tissue response, but, since there is no clue regarding their nature, no more can be said about them. It will be seen that the picture built up of the delayed response is hazy, imperfect, and based on fragmentary evidence. This is particularly unfortunate, because it is this type of response which seems to be inhibited by A.C.T.H. and cortisone. Such an inhibition is indicated by the effects of these substances on the tuberculin response and that to manganese butyrate. Such an inhibition would account for the therapeutic effect of these substances on infective asthma and on contact dermatitis, and possibly their effect on rheumatoid arthritis, polyarteritis nodosa, and inflammatory diseases of the eye, amongst others. Such an effect would account for the advance of tuberculous infection without tissue reaction (Hart and Rees, 1950) and for that bugbear of therapy with these substances, the development of septicaemia without the common associated subjective and objective disturbances. It is to be noted that a direct effect of cortisone on a hypersensitivity mechanism is not necessarily implicated.

Conclusion

This, then, is the hypothesis of the action of A.C.T.H. and cortisone that I want to present. It is not my hypothesis, it is the hypothesis which has developed as a result of the experiments and discussion of the workers on my unit. It will be recognized that it is based on very imperfect evidence, and the growth of knowledge may require it to be discarded. But, since the function of hypothesis is to stimulate experiment, there are one or two more fascinating features that may be admired before this beautiful hypothesis is slain by some ugly fact.

In the immediate type of allergic reaction the antibody is known to be present outside the cell, since sensitivity can be transferred passively by plasma. Perhaps antibody is adsorbed on the surface of the cell membrane and it is the sudden contact with antigen that releases histamine and other substances. In this immediate type of response the effective substances probably exist preformed in the cell. In the delayed type of reaction, antibody is not known to exist outside the cell, but it is presumably present inside, since plasma will not, while cells will, transmit sensitivity. Presumably, then, in this type of reaction antigen must penetrate the cell membrane before it can react with antibody to initiate the response. Moreover, in this delayed type of response it seems probable that the effective substances released do not exist preformed in the cell but have to be made. The delay may thus be due to the sum of the times taken for antigen to penetrate the cell membrane, to release an enzyme, and for that enzyme to complete its work. If this is a correct interpretation of the process, A.C.T.H. or cortisone may act at any of these points, and we are now trying to find out which.

Long, Miles, and Perry (1951) have put forward a hypothesis concerning the action of cortisone in reducing tuberculin sensitivity in the guinea-pig. They have shown that ascorbic acid reduces tuberculin sensitivity, but that this effect is inhibited by a factor present in cabbage. The desensitizing action of A.C.T.H. and cortisone is indirect and depends on a reversal of the cabbage effect. Since they find that the first oxidation product of ascorbic acid, dehydroascorbic acid, also desensitizes, they suggest that the cabbage factor prevents the oxidation of ascorbic acid. The desensitizing effect of cortisone is thus through facilitation of the oxidation of ascorbic to dehydroascorbic acid. This interesting hypothesis has yet to be put to the test in man.

Finally, what has all this got to do with the aetiology of allergic diseases? We don't know. But I must mention the recent work of Venning, Johnson, and Rose (1951). These workers estimated the excretion of three types of adrenal steroids in the urine of 38 patients with rheumatoid arthritis and 12 patients with asthma before, during, and after the therapeutic administration of A.C.T.H. Before treatment the mean excretion of each type of adrenal steroid was lower in asthma and much lower in rheumatoid arthritis than in normal subjects. A.C.T.H. produced a rise to or beyond the normal range, with an improvement in symptoms. In those with a very low steroid excretion initially, A.C.T.H. produced a rise to within the normal range. Since patients with Simmonds's disease and Addison's disease do not seem to suffer from asthma or rheumatoid arthritis it is unlikely that these diseases are due simply to a pituitary or adrenal defect; but this work suggests that such a defect may contribute to the aetiology of these conditions (see also Pearse, 1950).

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ACCUMULATION OF DIETHYLAMINOETHANOL ESTER OF PENICILLIN IN INFLAMED LUNG TISSUE

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Since the inception of widespread penicillin therapy, attempts have been made to dispense with frequent intermittent injections of aqueous solutions of penicillin salts by injection in an oily medium or as water-insoluble salts such as procaine penicillin. With the same end in view it was suggested that penicillin esters, by virtue of their greater stability and slower absorption and excretion, might offer some advantage (Meyer, Hobby, and Dawson, 1943). It was subsequently found, however, that the methyl, ethyl, and benzyl esters investigated at that time were unlikely to have therapeutic value in man, since no hydrolysis took place in the human body, although the esters of penicillin were effective in the treatment of experimental infection in mice, rats, and guinea-pigs (Richardson *et al.*, 1945; Ungar, 1947).

More recently, Carpenter (1948) prepared a dimethylaminoethyl ester hydrochloride of penicillin, which was readily hydrolysed *in vitro* in aqueous buffer at *p*H 7.3. Jensen *et al.* (1950) have subsequently reported that after injection of the analogous diethyl ester into guinea-pigs higher levels of penicillin can be detected in the lungs than in the blood at the corresponding time, and Heathcote and Nassau (1951) reported effective levels in sputum of patients treated with this ester. This remarkable observation particularly attracted our attention in view of past experience of the accumulation of penicillin in inflamed tissue (Ungar, 1950).

In the present communication a short account is given of our laboratory findings with the hydriodide of the same ester ("estopen").

Properties of the Ester

While the free base is readily soluble in water the hydriodide is only sparingly soluble (about 1% at 20° C.). This compound was injected as aqueous suspensions. The ester is stable in dry powder form, but is hydrolysed spontaneously in aqueous solution, hydrolysis increasing with rise in temperature and *p*H. The hydrolytic process brings about a fall in *p*H to about 4, where the rate of hydrolysis is small. At *p*H 7.35 the ester has a "half-life" of about 30 minutes at 37° C.

The unhydrolysed ester is not attacked by penicillinase—for example, that produced by penicillin-resistant staphylococci—but in aqueous solutions de-esterification takes place and the liberated benzyl-penicillin is inactivated by the enzyme. Also, in the animal body the ester is without effect against bacteria producing penicillinase. Groups of mice infected with a lethal dose of penicillin-resistant *Staphylococcus aureus* were treated with benzyl-penicillin or with its ester; treatment was ineffective with either.

The ester is apparently slightly more toxic than is benzyl-penicillin, particularly to guinea-pigs. In the first experiments guinea-pigs were injected with 100,000 units in 0.5 ml. of saline, which occasionally caused immediate reactions in the central nervous system and subsequent death (within about 10 minutes of injection). Accordingly the standard dose was reduced to 50,000 units in later experiments. The toxicity after intravenous administration is entirely due to the ester linkage, for the components of the ester (benzyl-penicillin and diethylaminoethanol hydriodide) are non-toxic when injected together at equivalent concentrations.

The bacterial spectrum of the ester is identical with that of benzyl-penicillin. It has been shown, however, that the intact ester is biologically inactive until hydrolysis liberates free benzyl-penicillin.

In laboratory animals and in human volunteers parenteral injection of the ester was found to produce penicillin levels in the blood intermediate between those produced by the same number of units of benzyl-penicillin or of procaine penicillin. Rather less penicillin was recoverable from the urine after injection of the ester than after injection of the other two preparations. On injection of the ester there was some slight antidiuretic effect, especially in rats; it could also be produced by injecting an equivalent amount of diethylaminoethanol. After intramuscular injection of the ester into normal rabbits it was found that penetration into the cerebrospinal fluid occurred to the same extent as with the same dose of procaine penicillin. When administered orally to rabbits (200,000 units in 5 ml. of water by stomach tube) the ester produced levels in the blood similar to those in control animals given the same dose of penicillin by the same route. The levels in rabbits treated with benzyl-penicillin, however, appeared to persist for rather longer.

Distribution of Penicillin after Administration of the Ester

Levels in Blood, Lung, and Other Tissues

The plate assay method was used with *Staph. aureus* as the test organism, and an average of five readings was taken at each test level. An account of the methods of preparing extracts of organs and the technique used in inducing local lesions is being prepared for publication elsewhere.

Bronchopneumonia was induced in mice and guinea-pigs by intranasal instillation, under ether–chloroform anaesthesia, of two drops of a saline suspension of *Haemophilus pertussis*, which resulted in marked consolidation of the lung in two to three days. Table I gives the results of levels in normal and infected mice and Table II in guinea-

TABLE I.—*Mice Injected Subcutaneously with 5,000 Units of Penicillin in 0.2 ml. of Saline. Average of 10 Mice for Each Level*

	Penicillin	Tissue	Penicillin Levels (units/g.) at (hours): ½	1	2	4	6	10	12	16	22
Normal mice	Ester	Blood	267	108	28	7·5	0	Not tested			
		Lung	180	75	17	1·8	0	,,	,,		
	Procaine	Blood	160	150	9	3·2	0	,,	,,		
		Lung	87	66	18	1·2	0	,,	,,		
Infected mice	Ester	Blood	182	253	87	15	12	0·11	0	0	0
		Lung	141	411	198	63	31	1·64	4·6	0	0
	Procaine	Blood	171	214	152	27	9	0·1	0	0	0
		Lung	158	123	123	21	7	0·2	0	0	0
	Sodium salt	Blood	—	114	62	4	0·4	0·2	0	0	0
		Lung	—	176	96	6	2·4	2	0	0	0

TABLE II.—*Guinea-pigs; Dose 100,000 Units in 0.5 ml. of Saline Subcutaneously. Average of Three Guinea-pigs for Each Level*

	Penicillin	Tissue	Penicillin Levels (units/g.) at (Hours): ½	1	2	4	6	10	12
Normal guinea-pigs	Ester	Blood	26	22	44	22	5	0	0
		Lung	10	24	40	11	5	0	0
	Procaine	Blood	16	35	44	15	23	2·6	1·3
		Lung	9	18	13	5	5	0·6	0·3
Infected guinea-pigs	Ester	Blood	9	8	11	7	4	2·1	0
		Lung	60	91	36	13	5	1·5	0
	Procaine	Blood	12	10	15	6·5	8	1·5	0·4
		Lung	<6	<6	<6	6	5	0·4	0·2
	Sodium salt	Blood	6	35	6·6	1	<0·2	0	0
		Lung	0	17	4	1·6	<0·2	0	0

pigs, after injection of the ester and procaine penicillin. They indicate that after injection of the ester significantly higher penicillin levels are detectable in the lungs than in the blood of the infected animals, particularly during the first six hours. Animals treated with procaine penicillin show consistently lower lung levels than do those treated with the ester, though the levels in the blood and lung tend to persist longer in guinea-pigs; this can be explained by the lower solubility of the procaine salt (about 0.6% at 15° C.) and its greater ability to form depots.

It can be seen (Table I) that with penicillin sodium salt we secured a concentration effect in infected lungs of mice, but far below the levels and for a shorter period (two to six hours only) than after the injection of the ester.

Specific Concentration in the Lungs

Further experiments showed that after injection the ester was concentrated only in the lungs, and not in other tissues, of those suffering from lung infection (Table III). Mice infected intracerebrally (Kendrick *et al.*, 1947) (Table IV) or rabbits with exudate due to turpentine injections (Ungar, 1950) did not show any selective concentration of the ester at the inflamed site. Levels of penicillin in the other organs of animals injected with the ester were similar to those recorded after injection of procaine penicillin or penicillin sodium salt.

TABLE III.—*Distribution of Penicillin after Subcutaneous Injection of the Ester, 5,000 Units, in the Tissues of Normal and Lung-infected Animals. Average of 10 Mice for Each Level*

		Penicillin Levels in Units/g. of Tissue at (Hours):		
		1½	3	5
Normal ..	Blood	37	13	0·4
	Lung	11	5	1·5
	Liver	24	4	0·8
	Spleen	5	2	<0·5
	Kidney	82	18	<6
	Muscle	<6	5	0·6
Infected ..	Blood	90	10	3
	Lung	766	96	131
	Liver	25	4	<2
	Spleen	14	<3	<2
	Kidney	145	14	<3
	Muscle	22	1	2

TABLE IV.—*Distribution of Penicillin in Tissues of Mice Infected Intracerebrally with H. pertussis after Injection of the Ester and Penicillin Sodium Salt. Average of 10 Mice for Each Level.*

Penicillin	Mice	Tissue	Penicillin Levels in Units/g. of Tissue at (Hours):					
			1	2	4	7	12	15
Sodium salt (5,000 units)	Normal	Blood	24	94	0·8	0·8	0	0
		Lung	13	23	0	0	0	0
		Brain	0·8	1·4	0	0	0	0
	Intracerebrally infected	Blood	500	5..	1·5	8	2·2	0·6
		Lung	400	50	31	28	0	1·4
		Brain	32	36	12	34	0	1
Ester (5,000 units)	Normal	Blood	110	82	6·6	1·7	0	0
		Lung	56	35	3	0	0	0
		Brain	3	2	0	0	0	0
	Intracerebrally infected	Blood	123	216	10	1·7	1	0·8
		Lung	70	200	48	6·7	0	0
		Brain	7	9	5	3·4	0	0

In the intracerebrally infected mice there was, after injection of the ester, no increase in the concentration of penicillin in the lungs compared with the blood, nor was a selective concentration noticed in brain tissue. It should be noted that the blood and tissue levels of penicillin were higher in infected animals than in normal mice, irrespective of the type of penicillin used. It is therefore justifiable to conclude that the selective concentration of estopen is a specific property of lung tissue, particularly of diseased lung tissue, and is not shown to the same extent by any other organ. We observed that in our experiments the degree of concentration of penicillin in the lungs was directly related to the total dose of the ester injected and to the extent of the lesions in the lungs, and also that in mice recovered from a lung infection injecting the ester two to three weeks later still induced a marked concentration of penicillin in the lungs.

Mode of Action of the Ester

Having established this basic property of the ester, we have tried to discover its mode of action and the reasons for its selective concentration. Two points had especially to be kept in mind: (*a*) the structure of the penicillin ester, especially in relation to its pharmacological action and those of its components; and (*b*) the special nature of lung tissue in contrast with other organs and its peculiarities when inflamed.

It should be mentioned that there seems to be a species specificity for penicillin accumulation in the lungs. It was noticed that in normal guinea-pigs, rabbits, and rats higher levels in the lungs were recorded than in the blood in the first 30 to 60 minutes after injection of the ester, but that no such phenomenon was seen in mice.

Though no detailed theory can yet be advanced to explain the mode of action of the ester, because of the complexity of factors involved, certain aspects of the matter have been elucidated, of which a brief account follows.

On injection of the ester some of it dissolves (about 0.9% at 15° C.) and ionizes in the blood, circulating as PD^+ and I^- (P=benzyl-penicillin; D=diethylaminoethanol; I=iodine). The PD^+ (ester) enters the lung and is there fixed by tissue constituents, particularly in inflamed tissue, from which it is gradually released, hydrolysis of the ester link liberating free P^-. The lung constituent that first fixes the PD^+ may be increased in amount, or its activity may be altered by *p*H or enzymatic changes in infected lungs. The equilibria concerned can thus be suggested as follows:

Ester injected ——→ carried to the lungs
Ester+lung constituents ⇌ ester-tissue complex (1)
Free ester ——→ D+P (2)
Penicillin is removed by the kidney via the blood stream, therefore reaction proceeds thus ——→ in (2)
The ester-tissue complex ——→ ester+lung tissue components reaction will proceed in this direction if ester is removed, the liberated ester being hydrolysed as in (2).

The lung may therefore contain, at any given time after injection, the following entities: (1) intact ester (as hydriodide or free base); (2) ester complex with the lung constituents; (3) free benzyl-penicillin; (4) benzyl-penicillin-tissue complex; (5) diethylaminoethanol-lung-tissue complex; (6) free diethylaminoethanol; (7) free I^-.

The effect of diethylaminoethanol on benzyl-penicillin was investigated, since this compound is a common constituent of both estopen and procaine penicillin. Some of the action of the ester might be caused by the presence of the alcohol (see experiments with procaine esterases by Kisch, Koster, and Strauss, 1943), which could exert an independent pharmacological action (Hauschild, 1950).

In other experiments (of which details are also being prepared for publication elsewhere) we found that simultaneous administration of the alcohol and the benzyl-penicillin prolonged the circulation of penicillin in the blood of rabbits and guinea-pigs; but this was not due to delayed excretion of penicillin in the urine, although in rats an antidiuretic action of the alcohol was noticed. In independent experiments, using specially prepared salts of diethylaminoethanol and benzyl-penicillin, we found that the compounds behaved in the matter of lung concentration exactly as penicillin sodium salt, which indicated that the effect in the lungs is dependent on the intact ester link within the molecule. It occurred to us that the selective concentration of penicillin in the lungs might be due to the conditions of enzymatic hydrolysis of the ester in the lungs differing from those in other organs. Investigation was therefore made into the

esterase activities of tissues from a number of animals (mouse, rat, guinea-pig, and rabbit) and from man. The method of Knafl-Lenz as modified by Harrer and King (1941), in which the activity of the esterase is measured by the rate of hydrolysis of ethyl butyrate, was employed. The results showed that esterases varying in activity from species to species were present in lung tissues. Inflamed lung tissue, in contrast with normal, however, showed esterase activity decreased to about 50% per unit weight of tissue. It is probable that the reduction of esterase in the diseased lung is at any rate in part responsible for the longer persistence of the ester in these lungs than in the healthy ones.

Following the hydrolysis of the ester in tissues and in human blood by an ether-extraction technique, we found that the soluble ester was hydrolysed rapidly at *p*H 7.35 at 37° C., but the hydrolysis curve began to flatten out at about 60% hydrolysis. It was therefore evident that part of the ester was being protected from hydrolysis owing to its being bound on constituents of the inflamed lung tissue, particularly on proteins. Using a modification of the ultrafiltration method described by Sirota and Saltzman (1950) (for measurements with aureomycin) we found that benzylpenicillin was bound on the tissue to the extent of 23.5%, whereas the ester at the same unitage was bound to the extent of 71%. Of the blood constituents, globulin was the fraction that bound 50% more ester than it did benzylpenicillin. In addition, we ascertained that 1% globulin bound as much ester as did 4% albumin.

Discussion and Comments

We noticed in our experiments that the ester injected into animals suffering from bronchopneumonia gave consistently higher penicillin levels in the lung tissue than did procaine penicillin or soluble penicillin salts. In none of the other inflamed organs (brain or muscle exudate) was this phenomenon noticed, the ester behaving in this and other respects similarly to procaine penicillin. Heathcote and Nassau (1951) have shown in the sputa of patients treated with the ester effective concentrations of penicillin higher than any observed in the past after injection of benzylpenicillin or procaine penicillin.

The reasons for the selective accumulation of penicillin in the lung tissue are many. We have found that the rate of hydrolysis in the lung may be affected by the amount of esterase available, which decreases in inflamed lungs, thus presumably causing persistence of unhydrolysed ester. The antidiuretic action of the diethylaminoethanol can be demonstrated in animals, and this might have a contributory effect in prolonging the levels of penicillin in the lungs. A number of physico-chemical interactions between the ester and lung tissue probably play a significant part; one of these is the binding on tissue constituents, and we have shown that the ester was bound on the tissue proteins to a greater extent than was benzyl-penicillin. Although the binding of certain drugs on proteins (sulphonamides, acridines, metallic compounds, etc.) is reputed to result in a decrease of their biological activity, experimental evidence and clinical experience with antibiotics seem rather to indicate that with them the process is usually reversible and that the bound drug is gradually released.

We found that hydrolysis of the ester takes place more rapidly at *p*H 7.3 than in a more acid solution. The *p*H of acutely inflamed tissue is about 7.2–7.5, whereas in chronic inflammation the *p*H may fall to about 6.5 (Menkin, 1950). This fact may partly explain the better therapeutic effect in acute than in chronic inflammation of the lungs (Jensen *et al.*, 1950).

The lung is an organ with distinct anatomical and physiological characteristics. In lower animals and plants diffusion takes place through cell membranes, but in higher animals diffusion of certain substances occurs only across the microscopic spaces between the blood and pulmonary alveoli (Kety, 1951). It seems that the lungs have for many substances passing through the capillaries an absorptive capacity that might differ in certain species—for example, the affinity of lung tissue for Koch's bacillus. Bacteria, viruses, and insoluble particles (Markham and Florey, 1951) are known to accumulate in inflamed areas, and this phenomenon has been observed by a number of authors, particularly in inflammation of the lung. According to Aschoff (1926), monocytes accumulate during the process of phagocytosis in the lung capillaries and disappear from the blood circulation. Siegmund (1926) also reported many monocyte-fibrin thrombi in the lung veins, a phenomenon that obviously affects blood circulation and causes venostasis in the inflamed lungs. Accumulation of monocytes, disintegration of phagocytes, and venostasis in inflamed tissue together result in changes in the globulin–fibrinogen–albumin ratio. The degree of binding of drugs on tissue constituents (proteins, cells) will therefore vary, depending on the composition and activity of the tissue and also on the physico-chemical properties of the drug; moreover, the rates of gradual release from the bound condition will also vary correspondingly. It is known that in tissue exudates the total protein is over 3% (specific gravity over 1.018), but in some chronic lesions (tuberculosis) the protein content is only 0.1–0.5 g.%, in contrast with normal tissue transudates (protein content under 3% and specific gravity 1.006–1.015), which contain mainly albumin with only traces of fibrinogen. In exudates the proportions of globulin and fibrinogen are much increased. The lung being an organ with a wide net of capillaries, any inflammation there will cause a proportionately larger increase of the inflammatory exudate than in other organs, particularly in the early stages of inflammation, owing to an increase in the capillary permeability followed by mechanical obstruction of venous circulation (venostasis, lymphostasis, small venous thrombi) and to the pressure of the exudate. Any of the antibiotics circulating in the blood will diffuse into the inflamed tissue, will be taken up by the tissue constituents to a degree depending on their physico-chemical affinity, and will be slowly released as a result of venostasis. Probably different drugs will vary in extent of accumulation, depending on their molecular size and structure. In addition, the types of exudate, either acute or chronic, differing widely in their chemical composition and cell constituents will have a pronounced effect on the accumulation of the antibiotic.

Summary

Experiments on laboratory animals have shown that: (1) diethylaminoethylbenzyl-penicillinate hydriodide (estopen) is selectively concentrated in lung tissue, particularly when inflamed, the degree of accumulation being related to the extent of the lesions. (2) Selective accumulation is more pronounced with estopen than with procaine penicillin or the sodium salt of benzylpenicillin (3) The factors involved in this accumulation include the different chemical properties of the drug used and the specific feature of lung structure and function.

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TREATMENT OF HYPOPITUITARY COMA

BY

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Any patient with severe hypopituitarism is liable to have episodes of a particular type of coma. She may recover from the first few attacks, but ultimately one of them proves fatal. A detailed description of this coma has already been given (Sheehan and Summers, 1949), and only the main aspects need be summarized here. To save space, the recent literature will not be analysed in the present paper.

The coma does not usually develop until the hypopituitarism has been present for several years, though occasionally it has been reported as occurring within a few weeks after the destruction of the gland. In many cases it follows some minor infection, or attacks of vomiting and diarrhoea, or some surgical operation. The patient gradually becomes drowsy, and, within a day or so, stuporous. She then passes into deep coma, which is sometimes preceded by one or two convulsions. During the stage of coma she may lie in a rigid, curled-up position and resist interference, or she may be flaccid and unresponsive to stimuli. In many cases there is no pulse at the wrist, and the heart sounds are almost inaudible. The nose and extremities are cold to the touch, the face is pale, and there is no sweating. Occasional cases have pyrexia. Ketonuria is common.

The exact cause of the coma is unknown. Despite the relative uniformity of the clinical picture, there may be several different types of functional disturbance. Some of the patients are in severe hypoglycaemia, with blood sugars of 15 to 30 mg. per 100 ml.; others have blood sugars in the range of 50 to 70 mg., which is a common level in uncomplicated hypopituitarism. Some patients have normal blood electrolytes; a few have a large reduction in sodium and chloride levels. The functional disturbance in these latter cases can be interpreted either as evidence of acute adrenal insufficiency or merely as the result of the preceding attack of vomiting and diarrhoea. A third group of patients have pronounced hypothermia and bradycardia, and their condition is in many ways analogous to hibernation.

The degree of hypothermia can easily be overlooked in routine hospital practice where the temperature is taken with a clinical thermometer. The mercury column has rarely been shaken down below the lowest graduation, and, when the thermometer has not "registered," the patient is recorded by the staff as having merely a low normal temperature. The significance of this point was emphasized by two recent observations on patients with myxoedema (not hypopituitarism) who were admitted in coma to the hospital. They were reported to have normal temperatures as observed with a clinical thermometer. The rectal temperature was then taken by a thermometer from a bacteriological incubator, and was found to be 77° F (25° C.) in one case and 83° F. (28.3° C.) in the other.

It is not easy to assess the value of treatment of hypopituitary coma, because if the patients are left without treatment some of them recover from the coma spontaneously and some die. Thus the only indications of the efficacy of any particular treatment are the rapidity of the clinical response and the proportion of patients treated in this way who do show a rapid response. At present there is little or no information about the real effect of each line of treatment, and the opportunities of obtaining this information are not frequent. The usual method of treatment in cases erported in the literature has been to give a stock combination of all therapeutic agents which might theoretically be of use. Our plan was to give each patient a single line of treatment, and then to leave her for a few hours so that any response could be observed. In the cases in which no improvement resulted, a second line of treatment was tried. Clearly this method would not reveal synergistic effects of different treatments, but such synergy is quite hypothetical.

Present Observations

Nine examples of hypopituitary coma have been studied in eight patients during the past four years. All the patients had the typical syndrome of severe hypopituitarism due to post-partum necrosis of the anterior lobe. The duration of the illness was from 6 to 21 years. In all the cases the clinical diagnosis was made before any treatment was given for the coma. Two of the patients died, and the clinical diagnosis was confirmed pathologically. These patients were usually admitted as emergencies at times when full laboratory facilities were not available, so that treatment had in most cases to be begun without prior information of any biochemical disturbance which might be present.

The methods investigated in these patients were: (1) no therapy; (2) the administration of large doses of glucose, to treat any possible hypoglycaemia; (3) the administration of cortisone, with the object of correcting a possible acute deficiency of corticosteroid hormones; (4) the administration of sodium chloride and deoxycortone, in order to correct disturbances of electrolyte metabolism; and (5) direct treatment of the hypothermia.

Cases Having No Therapy

Two of the patients who were not very deeply comatose were left without any specific therapy but under careful observation. With rest in a warmed bed they gradually recovered in the course of two to three days. The possibility that the warmth may have contributed to their recovery must be seriously considered in view of the results obtained by active treatment of hypothermia.

Glucose

In one patient, in whom a severe hypoglycaemic coma had been produced by insulin, the intravenous administration of 100 ml. of 25% glucose solution produced a dramatic and complete recovery within a few minutes. This is a special case, but the literature contains several reports of patients with hypopituitarism who spontaneously developed coma associated with severe hypoglycaemia, and whose coma responded equally rapidly to intravenous glucose.

Four patients with spontaneous coma were given 1 to 2 litres of 10% glucose solution intravenously in the course of two hours. Two of these showed some improvement within a few minutes. Instead of lying flaccid they began to make spontaneous movements and resisted interference; when attempts were made to rouse them they became noisy but incoherent. With continued administration of glucose during the next two days both patients gradually returned to full consciousness. One of these patients had a blood sugar of 70 mg. per 100 ml. before the administration of the glucose; the blood sugar in the other patient is not known. In contrast to these beneficial results, two other patients were given intravenous glucose in similar large doses, but the coma remained quite unaffected. One of these had been under observation for two days before she

became comatose. During that period she had been given very large amounts of glucose, so that she had a blood sugar of 110 mg. per 100 ml. at the time the coma developed. The initial blood sugar of the other patient was not ascertained.

When any patient with hypopituitarism has been given a large amount of intravenous glucose she is liable to become seriously hypoglycaemic within a few hours after stopping the treatment. It is therefore important, in cases of coma treated with intravenous glucose, to continue this treatment for a couple of days and subsequently to keep a careful watch on the blood-sugar level.

Cortisone

As it is sometimes considered that the coma is due to a deficiency of the adrenal hormones which control glucose metabolism, two of the patients were given large doses of cortisone intravenously. The preparation used was the standard suspension of cortisone acetate in saline "for intramuscular injection only." It contains some unknown suspending agent and 1.5% of benzyl alcohol. The intravenous administration of particulate suspensions has well-known dangers, but the circulatory state of the patients was so poor that rapid absorption from an intramuscular injection could not be expected. The suspension was therefore given by an intravenous needle, and followed by about 50 ml. of glucose–saline in order to carry the hormone from the arm to the right side of the heart. The amount of suspension given in each injection was 5 ml., with a content of 125 mg. of cortisone acetate. This was repeated at half-hourly intervals; in one case the total dose was 375 mg. and in the other case 750 mg. There was no recognizable effect, either good or bad, on the coma or on the general clinical condition. One of the patients subsequently recovered after the use of a different treatment; the other remained in coma and died 24 hours later. At necropsy there were no lesions, such as thrombosis in small pulmonary vessels, to indicate that the intravenous injection of the particulate suspension had in fact had any harmful effect.

As yet there is no information to indicate whether cortisone would have any prophylactic effect if given during the few days before the onset of coma.

Testosterone

As testosterone is of considerable value in the treatment of uncomplicated hypopituitarism, the question arises whether it would be of any use in the treatment of coma. This particular application has not yet been studied. Testosterone does not seem, however, to have any prophylactic effect. One of the present patients had received intramuscular injections of 100 mg. of testosterone propionate once a week for five weeks before the onset of coma, the last dose being given 36 hours before the coma began.

Saline and Deoxycortone Acetate

One patient was given an intravenous injection of one litre of normal saline containing 30 mg. of deoxycortone, without any other treatment for the first three hours after admission in coma to hospital. This did not have any effect on her clinical condition, but she responded subsequently to intravenous glucose.

Another patient, who was in fact developing a hypothermic coma, had been given 30 mg. of deoxycortone daily for three days before the onset of the coma. There was no apparent prophylactic effect.

Treatment of Hypothermia

A recent case of hypopituitarism admitted in coma was investigated from the aspect of hypothermia. She was of the clinical type which is characterized by much facial oedema and which shows similarities to myxoedema. During the previous few months her general condition had responded to cortisone but not to testosterone. As the clinical thermometer did not register, the rectal temperature was measured with a bacteriological thermometer and was found to be 87° F. (30.5° C.). The mouth temperature was the same. There was no pulse, the heart sounds were almost inaudible, and the heart rate was 41 a minute. Respiration and skin circulation were similarly depressed, and the general picture was in some ways similar to that of the late stage of severe shock.

It was decided to raise the patient's temperature to normal. Any attempt to do this by means of hot-water bottles or electric blankets would probably have produced blistering, in view of the very sluggish skin circulation. The patient was therefore immersed to the chin in a bath of water at a temperature of 93° F. (33.9° C.), and the temperature of the water was gradually raised to 102° F. (38.9° C.) in the course of one and a half hours. During this period the mouth temperature gradually increased and the heart rate became more rapid. When the mouth temperature reached 95° F. (35° C.) and the heart rate 65 a minute the pulse returned at the wrist and the colour of the face became less ashen. When the mouth temperature reached 97° F. (36.1° C.) and the pulse rate 75 the patient began to show signs of returning consciousness; she made active movements and muttered incoherently. When the temperature reached 98.6° F. (37° C.) and the pulse rate 92 she had returned to full consciousness and spoke short coherent sentences. Her physical condition at this time appeared good. She was dried quickly and returned to a warm bed, where she fell asleep. During the next few days her temperature remained at levels of 97 to 98° F. (36.1 to 36.7° C.) without any artificial aids such as hot-water bottles. She remained mentally rather dull for two days, but then began to respond satisfactorily to the short course of cortisone therapy which was instituted.

On a subsequent occasion this patient was readmitted to hospital in an almost identical hypothermic coma, with a rectal temperature of 89° F. (31.6° C.). The same treatment was given, and she was fully conscious again within two hours.

Summary

The coma which complicates, and often terminates, hypopituitarism is associated sometimes with hypoglycaemia, sometimes with low plasma sodium and chloride, and sometimes with a severe degree of hypothermia which may not be recognized. In theory the treatment should be varied to suit the particular functional disturbance, but in practice it has usually to be begun on an empirical basis before the results of biochemical investigations are available.

Intravenous glucose seems to be of moderate value in some cases, even with normal blood-sugar levels.

A patient with very low temperature recovered rapidly and dramatically from the coma when her temperature was raised to normal by means of a warm bath. This treatment was employed successfully in a subsequent attack of coma. It seems to hold promise in cases with hypothermia.

Intravenous administration of cortisone, and of saline solution with deoxycortone, produced no recognizable improvement in the few cases in which they were tried.

In individual cases no prophylactic value was observed from testosterone given during five weeks before the onset of the coma, deoxycortone for three days, and large quantities of glucose for two days.

The present conclusions are based on a small number of cases, and can therefore only be tentative.

The cortisone used in this work was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Merck and Co., Inc.

REFERENCE

Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, 18, 319.

HYPOPITUITARISM WITH PITUITARY TUMOURS

CORTISONE IN THE TREATMENT OF STUPOR ASSOCIATED WITH HYPOPITUITARISM

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The incidence of hypopituitarism associated with tumours in and around the pituitary fossa is difficult to assess on account of changing criteria of diagnosis. With the development of tests, such as the insulin sensitivity, the estimation of the urinary 17-ketosteroids and 11-oxysteroids, tests of radioactive iodine uptake, and Thorn's test of the eosinophil response to the injection of 25 mg. of A.C.T.H., it is now possible to make a more accurate appraisal of the endocrine state of these patients and to predict the likely response to stress. In Grant's (1948) series of 71 patients with intrasellar tumours, in the pre-operative period, 65 (91%) had evidence of hypopituitarism, whereas Davidoff and Feiring (1948) found amenorrhoea or failure of potentia in only 50 out of 93 cases (57%).

From a study of the post-operative mortality in pituitary tumours some writers suggest that one of the chief causes of death may be an endocrine failure. In Grant's series of 71 cases with 85 operations, 8 deaths occurred (11.2%). Six of these "had burned out chromophobe adenomata with polyglandular function which was at a very low ebb." In three of them Grant records that following a relatively simple operation the patients became stuporous and semicomatose and died on the fifth, ninth, or twelfth post-operative day. Necropsy done on two of these patients showed atrophy of the adrenals, thyroids, and gonads. He comments that "a simple evacuation of the tumour was enough to abolish completely what little pituitary function remained." He believes the operative mortality in these cases of generalized glandular insufficiency is high, and surgical attack should be undertaken cautiously. He writes: "A satisfactory test for adrenal insufficiency would be of value so that surgical measures could be avoided in cases with severe adrenal cortical damage."

Roche, Thorn, and Hills (1950) utilized the eosinophil levels during and after surgery, and their response to A.C.T.H., as a method of assessing the adrenocortical function. They concluded that the measurement of the fall in eosinophils after the injection of 25 mg. of A.C.T.H. prior to surgery was a good index of the capacity of the adrenal cortex to secrete 11-oxysteroids and furnishes a means of pre-operative prognosis.

The object of this communication is to place on record details of four patients with pituitary tumours with varying degrees of hypopituitarism, and to comment on their endocrine state and on their reaction to the stress of operation. In assessing the endocrine state of these patients we have relied on the history, the clinical state, the insulin sensitivity test, and the estimation of the urinary 17-ketosteroids as used by Fraser and Smith (1941). These authors found that patients with marked hypopituitarism have very low urinary 17-ketosteroids, and insulin-sensitivity curves which show a prompt fall of blood sugar and thereafter manifest hypoglycaemic unresponsiveness.

Case 1

A case of craniopharyngioma, with bitemporal hemianopia and marked hypopituitarism. After operation the patient passed into a drowsy semicomatose state, from which he slowly recovered without substitution therapy six weeks later, and in three months was discharged.

A single labourer aged 44 had noticed an increasing lethargy for five years, and for two months was unable to see objects on his left side. For a month he had complained of occipital headaches. His growth of hair on the face had always been sparse, and he had never shaved more than every other day. He had recently noticed failure of potentia and loss of libido.

On physical examination he was seen to be a well-nourished man with soft sallow skin having a tendency to dryness. His head hair was natural and his facial and body hair sparse. The axillary hair was scanty, and the pubic hair lacked curl and was of a female type of distribution. The optic disks were pale, and there was bitemporal hemianopia. His visual acuity was: left eye J 8, right eye J 6. A radiograph of the skull showed an enlarged sella turcica with erosion of the clinoid processes. An encephalogram revealed a rounded tumour arising from the enlarged sella turcica and indenting the third ventricle. A blood count showed: red cells, 4,130,000; haemoglobin, 11.46 g.; white cells, 6,650. The cerebrospinal fluid was under normal pressure and the contents were normal. The glucose-tolerance test gave 80, 110, 100, 100, 90 mg. per 100 ml. His blood pressure was 116/70.

On April 13, 1951, one of us (A. J.) did a right frontal craniotomy and an intracapsular removal of a craniopharyngioma. There was no intracapsular haemorrhage. On the day after operation he was restless and confused. His temperature and pulse were normal. There was no polyuria. He remained in a drowsy stuporous state, moving about in bed and replying indistinctly to questions. He was able to obey simple commands. His blood pressure was 100/60. His spinal-fluid pressure was 100 mm.; the fluid was xanthochromic; and the protein 160 mg. per 100 ml. Intravenous and intragastric glucose-saline was given, but he failed to rouse. On April 18 it was decided to explore the operation site again to exclude an extradural or subdural clot.

Operation revealed a small firm blood clot between the bone and the dura, and there was a minimal amount of clot beneath the frontal lobe. Following operation there was little improvement, and 36 hours later he was still in the same drowsy stuporous state and was more difficult to rouse. He was doubly incontinent. He made some response on painful stimulation. The spinal-fluid pressure was 100 mm. On April 21 exploration was again made. The frontal lobe appeared to be shrunken, but no blood clot was evident. He failed to rouse after the exploration, and six days later was still semicomatose and difficult to rouse. The total non-protein nitrogen was 24 mg. per 100 ml., serum sodium 342 mg. per 100 ml., serum potassium 16 mg. per 100 ml. The electrocardiogram was within normal limits. He remained in this drowsy semicomatose state for five weeks; then he began to rouse and gradually improved, regained sphincteric control, and a week later was able to get up in a chair. He improved steadily, and on July 11 was discharged. His visual acuity was: right eye

J 1, left eye J 2; and to confrontation there was a left upper quadrant defect. He had a complete amnesia for a period of five weeks after the initial exploration.

Case 2

A case of chromophobe adenoma causing visual-field defects and marked hypopituitarism. Following operation he passed into a stuporous state and actively refused food and fluids. Substitution therapy with testosterone, D.C.A., thyroid, and salt was started. A week later he was much improved. Discharged well.

A bus contractor aged 47 was admitted to the Dunedin Hospital on account of failing vision. Fifteen years previously he had had a severe bout of headache which settled in a week or two. He remained well until eight months before admission, when he noticed his vision was defective. He had never had a normal amount of hair on his chest and his facial hair was sparse at the sides. All axillary hair had fallen out over the past year and his pubic hair was very scanty. For a year there had been loss of libido and failure of potentia.

On examination he was seen to be a sallow-complexioned, well-developed, well-nourished man with a full head of fine hair, sparse hair on the sides of his face, sparse hair on the limbs, and none on the chest. There was complete lack of axillary hair, and his pubic hair lacked curl and was sparse and of a female type of distribution. The gonads were small and soft, the prostate small. His hands and feet were large. His visual acuity was J 2 in each eye. Both optic disks were white, with clearly defined edges. To small objects he had a complete bitemporal hemianopia with sparing of fixation-point. The rest of the central nervous system and other systems were normal. The blood pressure was 110/70. A radiograph of the skull showed a greatly enlarged pituitary fossa. An encephalogram showed the third ventricle and basal cistern to be filled and the tumour outlined. It appeared to be larger on the left side. A blood count showed: haemoglobin, 13.6 g.%; packed cell volume, 41%; white cells, 7,100 (eosinophils 125 per c.mm.). The blood and spinal fluid Wassermann reactions were negative. The spinal fluid was under normal pressure; there was a moderate increase of globulin; total protein, 70 mg. per 100 ml. The glucose-tolerance curve was flattened—70, 80, 90, 90, 100 mg. per 100 ml. The insulin-sensitivity curve (0.1 unit of insulin per kg.) was 70, 30, 25, 30, 40, 55 mg. per 100 ml. and showed marked hypoglycaemic unresponsiveness. The serum cholesterol was 295 mg. per 100 ml., and the urinary 17-ketosteroids 0.5 mg.

One of us (A. J.) did a left frontal craniotomy and removed a chromophobe adenoma. The patient failed to rouse in a normal fashion and remained drowsy and stuporous but could be got to answer questions. On the third post-operative day he was very restive and forcibly refused any fluid or food intake. This active refusal necessitated feeding by tube. He was incontinent of urine and faeces and continued in a stuporous state with a negativistic attitude, making nursing care difficult. His blood pressure was 104/64. The blood sugar was 115 mg. per 100 ml., and there was no sweating, tachycardia, or vomiting. The serum sodium was 230 mg. per 100 ml., and serum potassium 16 mg. per 100 ml. Two weeks after operation he was in much the same state and the double incontinence persisted. He was then given an implant of testosterone, 200 mg., and 100 mg. of D.C.A. Sodium chloride, 2 g., and thyroid siccum, 1½ gr. (0.1 g.), were given daily. His blood count was: red cells, 4,000,000; Hb, 11.9 g.%. Six days after the implants he was much improved, and was continent and co-operative and eating food normally. His temperature was normal and there was no excessive thirst. He was still drowsy and had a partial amnesia for two weeks in the post-operative period. His skin was dry and showed a branny desquamation on the face and limbs. He was discharged 40 days after the operation feeling well and more energetic than before operation. His visual acuity was: right eye J 2, left eye J 1. There was still an upper quadrant defect in both temporal fields.

Case 3

Chromophobe adenoma of the pituitary gland with bitemporal hemianopia and hypopituitarism. Patient failed to rouse after operation. Possible response to cortisone and "neosynephrine," with complete recovery.

A builder aged 46 was admitted on September 14, 1951, complaining of failing vision. Four years previously he had noticed difficulty in seeing objects on the left side, and thereafter the vision in the left temporal field gradually deteriorated. Three years previously he developed left frontal headaches, which were worse in the morning and throbbing in character. These cleared after several weeks. His skin had always been soft and his body hair scanty. He shaved daily, but his facial hair was sparse. His potentia and libido had never been notably good, and recently had failed completely.

On examination he was seen to be a well-developed and well-nourished man with sallow skin which was puffy about the face and wrinkled round the mouth. His head hair was fine and facial hair sparse. There was complete loss of axillary hair, and his pubic hair was scanty and of female distribution. There was very scanty hair on the limbs and chest. The eyebrows were normal. The gonads were small and soft on palpation. The visual acuity was: left eye 6/12, right eye 6/6. To confrontation tests there was a complete left temporal hemianopia and a partial right hemianopia. The disks were pale on the temporal halves. The rest of the central nervous system was normal. The heart was enlarged. The aortic second sound was accentuated, and the blood pressure was 190/120. The spinal-fluid pressure was 140 mm.; and there was no increase of cells; protein, 60 mg. per 100 ml. The Wassermann reaction was negative in the blood and spinal fluid. A radiograph of the skull revealed a considerable enlargement of the sella turcica and a few small flakes of calcium above and in front of it. The serum cholesterol was 305 mg. per 100 ml.; haemoglobin, 11.6 g.%; P.C.V., 36%; white cells, 6,000 (eosinophils 225 per c.mm.); glucose-tolerance test, 80, 110, 90, 90 mg. per 100 ml.; the insulin-tolerance curve (0.1 unit of insulin per kg.) was 75 mg. resting, 35, 35, 30, 30, 50, 65 mg. per 100 ml. Hypoglycaemic symptoms developed 20 minutes after the injection of insulin. The urinary 17-ketosteroids were 0.3 mg.

On September 24, 1951, one of us (A. J.) did a right frontal craniotomy and partially removed a chromophobe adenoma. The patient failed to rouse completely, and 36 hours later was confused, disorientated, and incontinent. He became increasingly drowsy, but could be roused by shouting, and he answered questions. Pulse and respirations were normal, temperature 103° F. (39.4° C.). It was possible that his state was due to a crisis of hypopituitarism, but post-operative haemorrhage could not be excluded and the right frontal flap was again turned down. A small amount of clot was removed from the vicinity of the pituitary fossa. In the second post-operative period he failed to rouse, and again the frontal flap was turned down and a small clot removed. On September 27 the serum sodium was 294 mg. per 100 ml., serum potassium 21 mg. per 100 ml., and blood sugar 120 mg. per 100 ml. The electrocardiogram did not reveal evidence of abnormal potassium level. His pulse was 158, blood pressure 100/70, and respirations 80. Cortisone therapy was started on September 27 with 100 mg. intramuscularly, and 0.5 ml. of neosynephrine was given and repeated two-hourly. Thereafter 50 mg. of cortisone was given six-hourly.

Forty-eight hours after cortisone and neosynephrine were begun there was a notable improvement in his condition. The temperature settled and he became more alert and noticed things around him. The blood pressure rose to 160/90. On September 30 the cortisone was reduced to 10 mg. six-hourly and 10 units of A.C.T.H. was given twice daily. On October 2 the cortisone and A.C.T.H. were discontinued. Next day his wound flap was found to be

infected with a coagulase-positive *Staphylococcus aureus*, but his general condition was very satisfactory. He had an amnesia for the duration of the crisis. On October 13 he was given two pints (1.14 litres) of blood, implants of 200 mg. of testosterone and 100 mg. of D.C.A. were made, and thyroid siccum, 1½ gr. (0.1 g.) daily, and sodium chloride, 2 g., were started. On October 21 he was feeling well but still had a freely discharging sinus in the scalp wound. The heart was probably enlarged. The blood pressure was 160/100 and the blood sugar 255 mg. per 100 ml. On November 30 his general condition was very good, and the right visual field was normal. The left temporal hemianopia still persisted. Osteomyelitis developed in the bone, which was excised, and complete healing followed.

Case 4

A case of acromegaly and chromophobe adenoma. After operation the patient failed to rouse. Re-exploration done, without improvement. Cortisone therapy started, with marked improvement in 28 hours.

A clerical worker aged 39 was admitted to the Dunedin Hospital on November 2, 1951. In 1939 he was often prostrated with severe bitemporal headaches; he had to consult a dentist on account of difficulty with his bite, and he had some trouble with his vision. Eight years ago he noticed difficulty of vision on the left side. This was first apparent when playing cricket, and he was forced to alter his stance as he was unable to see balls coming on the leg side. Although he noticed no change in his appearance, his family state that on his return from the second world war he was hardly recognizable on account of the gross changes in his face. His mother stated that at this time he was always tired and limp and ready to sleep. There had been relative loss of potentia and libido for a year or more. He shaved daily.

On examination he had all the classical features of a gross acromegaly with advanced changes in the face and upper and lower extremities. There was a kyphosis in the upper thoracic region, and he had almost complete bitemporal hemianopia with macular sparing. His visual acuity was 6/6 in each eye. There was pallor of both disks. The secondary sex characteristics were normal. Growth of facial and body hair was normal. The spinal-fluid pressure was 120 mm.; protein 60 mg. per 100 ml. An *x*-ray film of the skull revealed a very large sella turcica. Other skeletal changes were characteristic of acromegaly. An encephalogram showed evidence of extension of the tumour upwards and backwards. The Kepler test was normal. Factor A, 77. Serum sodium, 330 mg. per 100 ml.; serum potassium, 18.3 mg. per 100 ml. The glucose-tolerance curve was flattened—90, 110, 90, 70 mg. per 100 ml. The insulin-sensitivity curve, 90 mg. resting, 75, 70, 75, 80, 85 mg. per 100 ml., showed some insensitivity. P.C.V. 39%; haemoglobin 11.6 g.%. The electrocardiogram was within normal limits. The blood pressure was 128/74. The urinary 17-ketosteroids were 5 mg.

The pre-operative diagnosis was acromegaly and eosinophilic adenoma of the pituitary gland, which shows some evidence of being "burnt out," as the biochemical findings suggested some hypopituitarism. On November 19 one of us (A. J.) carried out a right frontal craniotomy and aspirated mucoid material from a large pituitary tumour. The patient regained consciousness half an hour after the operation was completed, but the following day was drowsy and difficult to rouse and had a tendency to vomit. He became increasingly drowsy, but could be roused if spoken to loudly and would obey commands. As the drowsiness was increasing it was decided to re-explore the operation site. An unimportant quantity of subdural clot was removed and the tumour capsule was full of blood clot but was not under tension. After operation he failed to rouse. There was no sweating or vomiting; the pulse was 100. The blood sugar was 115 mg. per 100 ml., the total N.P.N. 34 mg. per 100 ml., the serum sodium, 297 mg. per 100 ml., and the serum potassium 16.5 mg. per 100 ml. The blood pressure was 100/60.

Cortisone therapy was started, 50 mg. intramuscularly six-hourly. Twenty-four hours later his condition had deteriorated further and he could not be roused. Cortisone, 100 mg., was then given, and two hours later he roused and asked for a drink; thereafter he made steady improvement. He had an amnesia for the period of the crisis. Cortisone, 40 mg., was given six-hourly for four more days. On November 29, implants of testosterone, 200 mg., and D.C.A., 100 mg., were made, and thyroid, 1½ gr. (0.1 g.) daily, and sodium chloride, 2 g., were started. He made steady progress until the date of his discharge. The visual-field defect was improved.

Discussion

Each of these patients had a pituitary tumour—three a chromophobe adenoma and one a craniopharyngioma. Three showed clinical and biochemical evidence of advanced hypopituitarism, and the patient with acromegaly had clinical and biochemical evidence of partial hypopituitarism.

Assessment of the Degree of Hypopituitarism

Clinical.—In three of the patients the history was suggestive of a degree of hypopituitarism for years before the local signs of an intracranial tumour developed, as evidenced by scanty growth of body and facial hair, fine head hair, and lowered potentia and libido. In these three there had been recent falling of axillary and pubic hair, a reduced tolerance to cold, and a failure of potentia and loss of libido. On examination all were well developed and well nourished, with fine head hair in three and normal hair in the patient with acromegaly. The hair on the side of the face was sparse, body hair was sparse with complete loss of axillary hair, and the pubic hair was of a female type of distribution in Cases 1, 2, and 3. In Case 4 the body and facial hair was normal. In Cases 1, 2, and 3 the skin appeared slightly oedematous and sallow, and was wrinkled about the mouth. The testicles were small and soft in Cases 1, 2, and 3.

Laboratory Assessment.—In this our chief guides were the insulin-sensitivity test and the estimation of the urinary 17-ketosteroids. The insulin-sensitivity curves in Cases 2 and 3 were typical of hypopituitarism. In Case 4 the curve suggested a residual insulin resistance (see Table). In Cases 2, 3, and 4 the urinary 17-ketosteroids were 0.5 mg., 0.3 mg., and 5 mg. respectively.

Insulin Sensitivity (mg. per 100 ml.)

Case	Resting Blood Sugar	20 min.	30 min.	60 min.	90 min.	120 min.
2	70	30	25	30	40	55
3	75	35	35	30	30	65
4	90	75	70	75	80	85

It is apparent that Cases 1, 2, and 3 were in a state of advanced hypopituitarism before operation and that Case 4 was less so. In Case 1 the evidence of advanced hypopituitarism was apparent from the history and from the clinical examination. In Cases 2 and 3 the history, clinical examination, and laboratory tests all indicated that these men were in a state of advanced hypopituitarism. In Case 4 it was evident from the acromegaly that there had been overactivity of the eosinophil cells, but the low excretion of 17-ketosteroids strongly suggested that the patient had passed to a state of hypopituitarism, although the insulin-sensitivity curve still showed some evidence of insulin resistance.

These patients suffered from a form of stupor with altered consciousness and disorder of behaviour of varying duration following pituitary operations. In this state of stupor the patients lay quietly, the pulse was normal, the blood pressure was low, and the temperature was elevated in one and normal in three. The corneal reflexes and all superficial

and deep reflexes were present and natural. All could be roused by shouting or by painful stimulation, and at times they obeyed simple commands. There was marked confusion and disorientation, and one actively refused food and fluids. Incontinence of urine and faeces was common to all, but no grasping, groping, or other primitive reflexes were observed. After recovery there remained a period of amnesia for the duration of the stupor.

Treatment and Complication

Allott and Simmons (1951) reported the effect of cortisone in a crisis in one patient with Simmonds's disease. In their record the patient had passed into the state of crisis spontaneously. A state of hypoglycaemia was present, but in spite of intravenous glucose-saline the patient failed to rouse until cortisone was given: thereafter improvement was apparent in 24 hours, and after four days she had emerged from the crisis.

In our first patient no substitution therapy was attempted and the state of stupor persisted for 35 days. Thereafter there was steady improvement. In Case 2 substitution with testosterone, D.C.A., and thyroid was begun on the sixteenth day of the stupor and six days later he recovered consciousness. In Case 3 the crisis was resolved with a short course of cortisone (720 mg.) and A.C.T.H. (60 units intravenously) beginning on the third day of cortisone therapy, and improvement was marked in 48 hours, with a fall of temperature, return of orientation, and recovery of the sphincteric control. In Case 4, cortisone therapy was begun on the third day, and 26 hours later he roused and thereafter made steady progress. In this case the total cortisone administered was 1.04 g. in six days. Subsequently, Cases 3 and 4 had implants of testosterone and D.C.A., and thyroid was started.

Complications of cortisone therapy have been reported by several authors. Summers and Sheehan (1951) have reported some cerebrovascular accidents during cortisone therapy. In our third patient osteomyelitis developed in the bone flap, and it is possible that he was predisposed to this infection by the cortisone therapy, as has been shown by other authors. For these and other reasons we believe that the administration of cortisone should be reserved for a short course of therapy in this state of stupor associated with hypopituitarism, and that for more prolonged substitution, testosterone, D.C.A., and thyroid are adequate.

In an attempt to explain the mechanism of the state of stupor we have described, several possible mechanisms have to be considered. The condition presents with an acute psychopathology, an altered state of consciousness, and some behaviour disorder. It may be due to a localized cerebral lesion situated in the frontal lobes or in the hypothalamus, or it might be an expression of a generalized cerebral defect due to hypoglycaemia, hypokalaemia, or to an endocrine failure, either local or generalized.

The handling of the frontal lobe during operation might be a cause of altered consciousness with incontinence. It is to be noted, however, that no primitive reflexes were elicited in these patients as might be expected if the lesions were in the frontal lobes.

Damage to the hypothalamus in the experimental animal and to the intramedullary or extramedullary lesions in man will give changes in sleep, consciousness, and behaviour. Some recorded cases have not been associated with endocrine dysfunction and have been reversed by operation (Cox, 1948). In addition Riddoch *et al.* (1938) have stated that "it is often impossible to assess the origin of certain symptoms which are common to lesions of both hypophysis and hypothalamus."

More recent observations by Williams and Parsons-Smith (1951) suggested that in stupor the inactivity results from disturbances in the ascending reticular system, which is concerned with the activation of afferent impulses. A degree of operative trauma in this region during operation is no doubt sustained, and this system might well have been damaged.

If we accept Selye's doctrine of the adaptation syndrome, then it is clear these patients with failure of the pituitary and secondary failure of the adrenal and other end-organ function are deprived of their protective mechanisms and are in no condition to respond to the stress of an intracranial operation. The state of stupor then may be the outcome of this general endocrine failure. The endocrinological and nervous functions are to some extent dependent on each other, and we believe the somewhat dramatic response to cortisone and other substitution therapy lends support to the theory of general endocrine failure.

In view of the secondary failure of the adrenal glands it would not be surprising to discover a state of crisis which resembles the crisis of Addison's disease. It is noted that moderate hypotension was common to all cases, and also that the serum sodium levels were just below normal in three of the patients. In none, however, was there vomiting, sweating, or a state comparable with the crisis of Addison's disease.

Patients with hypopituitarism are prone to attacks of hypoglycaemia on account of their increased sensitivity to insulin, defective gluconeogenesis, and their resultant hypoglycaemic unresponsiveness. In none of our patients did the state of crisis resemble that of hypoglycaemia. In Allott and Simmons's patient, quoted above, a state of hypoglycaemia was present in the crisis. In our cases there was no sweating, tremor, or tachycardia, and the blood-sugar levels in three were normal.

Allott (1939) and Cooper and MacCarty (1951) describe cases that developed raised serum sodium and blood chlorides and low urinary chlorides following intracerebral operations. In two of the latter's cases the electrolytic abnormalities followed surgical removal of pituitary tumours. No detailed account is given of the endocrine state of these two cases before the operation, but the clinical description of the condition of the two patients in the post-operative phase was comparable to that seen in our four patients. In our patients, however, the serum sodium levels were lowered in three and normal in one.

The evidence obtained from these cases is not complete enough to establish with any certainty whether one or several factors were operating. From the therapeutic response to substitution, a further means of investigation is available, and the results suggest that endocrine dysfunction may predispose to a state of stupor and possibly death. If this is established in future cases prophylaxis against this state of crisis may be possible by substitution therapy in the pre- and post-operative periods.

Summary

Four patients with hypopituitarism associated with pituitary tumours are described.

The assessment of hypopituitarism by clinical and biochemical methods is discussed.

Following operation the four patients passed into a state of stupor. The nature of this stupor is discussed.

In two patients the stupor was effectively treated with cortisone and subsequent substitution with testosterone, D.C.A., and thyroid.

In one patient the stupor appeared to be relieved by substitution with testosterone, D.C.A., and thyroid.

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A.C.T.H. IN HYPOPITUITARISM

BY

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AND

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Hypopituitarism is a condition which presents a therapeutic challenge. In theory successful treatment demands the replacement of all the hormones of the anterior pituitary. At present there is no method of meeting this demand. In the past the most satisfactory treatment has been an attempt to compensate for the secondary atrophy of the gonads, the suprarenal cortex, and the thyroid by the use of testosterone, deoxycortone acetate, and thyroid extract. With the introduction of A.C.T.H. into clinical medicine there arose an opportunity of replacing at least one of the missing hormones of the anterior pituitary. So far there have been few reports on the use of A.C.T.H. in hypopituitarism. In recent papers Robertson and Kirkpatrick (1951) and Summers and Sheehan (1951) have reviewed the position and reported their own experiences. In most cases there was subjective improvement, but in the two cases described by Summers and Sheehan the picture was complicated by the occurrence of migraine and hemiparesis. The biochemical effects of treatment have been less constant. This paper reports the use of A.C.T.H. for short periods in three cases of hypopituitarism.

Case Notes

Case 1.—A man aged 62 had suffered from typical hypopituitarism for five years. The illness began with a period of severe headache, pyrexia, and stiffness of the neck. These symptoms lasted for three weeks and were succeeded by the signs of hypopituitarism. Presumably his pituitary was damaged by an infective lesion. His speech and movements were slow and his limbs stiff, he was perpetually sleepy, he had been impotent for five years, he had a very poor appetite, and was intensely sensitive to cold. He had mild angina of effort and may have had a small myocardial infarct one year previously. The skin was dry and the muscles were flabby. There was no hair on the chest or in the axillae; the pubic hair was scanty and the external genitalia had atrophied. The scalp hair was very fine and silky. The basal metabolic rate was −35%. An intravenous injection of 1.5 units of soluble insulin produced severe hypoglycaemic symptoms. The 17-ketosteroid excretion was 1.5 mg./24 hours.

Case 2.—A man aged 59 had a large sella turcica with erosion of the clinoid processes. For one year he had been very sensitive to cold, had had stiff legs, a hoarse voice, and a very poor appetite. He was apathetic, slow, and uncooperative. There was no hair in the axillae or on the chest, the testes had atrophied, and the pubic hair was scanty. His face was pale and the scalp hair very fine. The visual fields were unimpaired. The basal metabolic rate was −27% and the 17-ketosteroid excretion 1.9 mg./24 hours. Presumably he was suffering from a chromophobe adenoma of the pituitary.

Case 3.—A woman aged 48 suffered from a severe postpartum haemorrhage after the birth of her third child 16 years previously. Since then she had been tired and had slept a great deal. Lactation did not begin after delivery, and there had been only two brief episodes of vaginal bleeding in 16 years. She had been unconscious for 10 days after a minor operation 10 years ago. She spoke very slowly, had a poor appetite, was very sensitive to cold, and was apathetic but co-operative. The axillae were hairless, her face was pale, and the haemoglobin was 68% (Sahli). The 17-ketosteroid excretion was 3.3 mg./24 hours and the basal metabolic rate −35%. She was suffering from hypopituitarism due to a post-partum necrosis of the pituitary.

Treatment

In each case A.C.T.H. was administered for a period of 10 days after a control period of similar duration. Case 1 received a second course, for seven days, after a further control period. None of the patients had had previous hormonal therapy, and none received any other treatment during the time when A.C.T.H. was given. Case 1 received 25 mg. of A.C.T.H. by intramuscular injection twice daily, Case 2 had 25 mg. thrice daily, and Case 3 had 12.5 mg. four times daily. The A.C.T.H. was that marketed by Messrs. Armour under the name of "acthar."

Results

Subjective Changes.—In each case the most striking clinical result was a great subjective improvement. This took the form of a decreased tendency to fall asleep, the disappearance of much of the stiffness of the limbs, a more rapid speech, and a decrease in the sensitivity to cold. Case 1 felt hungry for the first time in five years. He was able to cut a caper on the floor of the ward, whereas he had only walked slowly and stiffly before having A.C.T.H. Case 2 changed from an uncooperative, apathetic, and rather surly fellow, who did not want to remain in hospital, into a grateful, helpful, and appreciative patient. Case 3 became loquacious and even a little argumentative instead of the dull silent woman she had been. She volunteered that she would like to go for a long walk, an idea that had not occurred to her for many years. These changes were much appreciated by the patients, who all said that they felt better than they had done for a long time. The improvement was not apparent for the first two days of treatment, but began on the third day and was maintained until about three days after the treatment ceased, when it began to decline. Testosterone and thyroid treatment was started before the relapse was complete.

Weight.—Both Cases 1 and 2 showed an increase in weight of 2 kg. during the second half of the period of treatment. In Case 3 the weight fluctuated considerably while treatment continued, but did not show an overall increase.

Clinical Signs.—No patient showed any considerable change in the pulse rate or blood pressure, though there was a small increase in the pulse pressure in Case 1. This patient developed slight ankle and sacral oedema on the last day of his treatment. At the same time his angina of effort was more easily produced. The electrocardiograph did not record any change in Cases 1 and 2. It was not used in Case 3. There was no significant alteration in the haemoglobin level of any patient.

Eosinophil Counts.—Fig. 1 shows the eosinophil counts in the three patients. The counts were done by the method of Roche, Thorn, and Hills (1950). They were made four hours after the first injection of A.C.T.H. each day during treatment and at the same time of day during the control period. In two patients there was a fall in the eosinophil counts. In Case 1 the fall began on the third day of treatment. In Case 3 it began on the seventh day. In Case 2 it is difficult to say whether or not a significant effect was produced, as unfortunately the number of counts performed before treatment was inadequate.

Capillary Resistance.—In Case 1 the capillary resistance was measured before, during, and after the second course of treatment by the method of Robson and Duthie (1950). The readings are shown in Fig. 2. There was a significant increase in the capillary resistance, beginning on the fourth day of treatment. These measurements were not made in the other two patients.

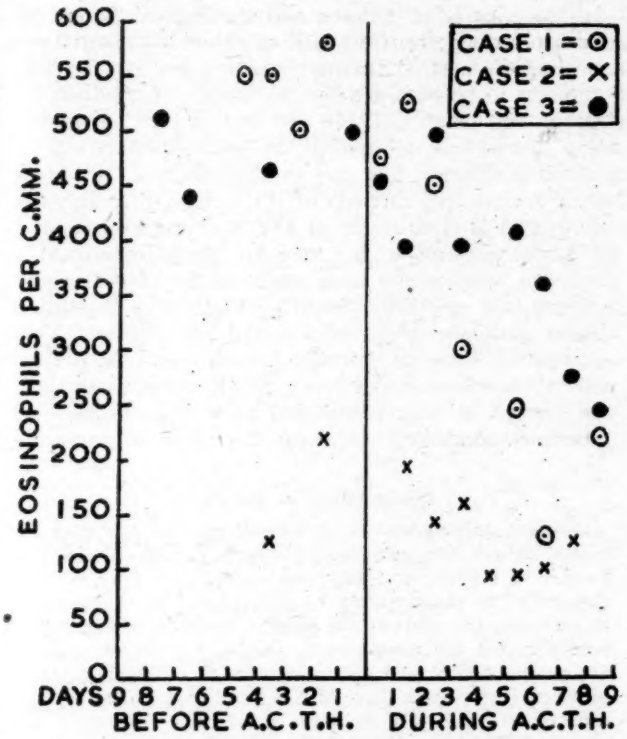

FIG. 1.—Eosinophil counts in three patients.

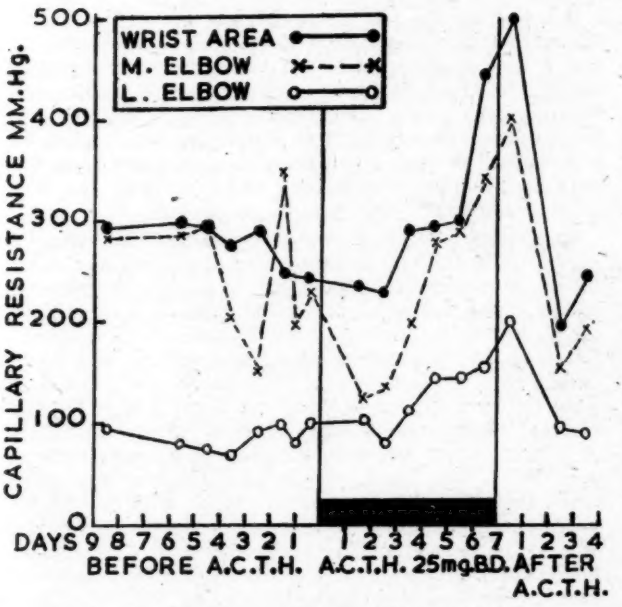

FIG. 2.—Capillary resistance readings in Case 1.

Carbohydrate Metabolism.—Insulin-sensitivity tests were done in Case 1. Capillary blood was used and the sugar was estimated by the method of Hagedorn and Jensen. In a test done before A.C.T.H. was given, an intravenous injection of 1.5 units of soluble insulin caused the blood sugar to fall from 105 to 44 mg. per 100 ml. in 30 minutes and produced severe hypoglycaemic symptoms, showing that the patient was very sensitive to insulin. On the tenth day of treatment with A.C.T.H. a larger dose of 2.5 units of insulin caused the blood sugar to fall from 114 to 74 mg. per 100 ml. in 45 minutes and produced no symptoms. This indicated a decrease in the sensitivity to insulin.

Glucose-tolerance tests were done before and during treatment in the three patients. The tests were performed in the early morning: 50 g. of glucose was administered by mouth, venous blood was used, and the estimations of sugar were made by the method of Hagedorn and Jensen. There was no constant change in the glucose-tolerance tests during treatment with A.C.T.H.

Hormone Excretions.—Urinary 17-ketosteroid levels were estimated in the three patients before and during treatment with A.C.T.H. by the method of Callow, Callow, Emmens, and Stroud (1939). In Cases 1 and 3 there was no significant change in the levels during treatment. Case 2 showed an increase from a daily average of 1.5 mg. before treatment to a daily average of 3.4 mg. during the latter half of treatment.

Chloroform-extractable formaldehydogenic corticoids were estimated in the urine of Cases 1 and 3 before and during treatment by a modification of the method of Daughady, Jaffe, and Williams (1948). Because of the known deficiencies of such methods (Marrian, 1951) it is thought to be inadvisable to publish any figures for the corticoid excretion. However, the estimations indicated that in Case 1 the urinary excretion of these corticoids was approximately doubled during treatment, while in Case 3 it was increased by about 50%. In Case 1 the increase began on the second day of treatment, and in Case 3 on the third day.

Conclusions

The subjective improvement in each patient was very striking. As A.C.T.H. is not known to have any action other than that of stimulating the adrenal cortex it is probable that these subjective changes were due to the action of adrenocortical hormones produced in response to the stimulus of A.C.T.H. Objective evidence of an increase in the production of adrenocortical hormones was obtained by some of the tests described. There was an increase in weight in two patients and a fall in the eosinophil count in two. The capillary resistance increased and the insulin sensitivity decreased in the one patient in whom these were measured. There was an increase in the urinary 17-ketosteroid excretion in only one of the three patients. The urinary corticoid excretion increased in the two patients in whom this was estimated. It is thus fair to conclude that the adrenal cortices of these three patients responded to the stimulus of a few injections of A.C.T.H. by increasing their output of steroid hormone.

The only undesirable effects produced were the development of slight oedema and the mild aggravation of the angina in Case 1. This might well have become more serious if the treatment had been continued. It is impossible to judge the value of a long period of A.C.T.H. treatment in hypopituitarism from the results in these patients, and further work will have to be undertaken for this purpose.

Summary

Three patients suffering from hypopituitarism were treated for periods of ten days with A.C.T.H.

In each patient there was a dramatic subjective improvement during treatment. Various objective signs of an increase in secretion of adrenocortical hormones were obtained, such as an increase in weight, a fall in eosinophil counts, a decrease in insulin sensitivity, an increase in capillary resistance, and an increase in urinary corticoid and 17-ketosteroid excretions.

In one patient oedema developed and a pre-existing angina was aggravated.

It is concluded that the adrenal cortices of these patients responded to the stimulus of A.C.T.H.

We are grateful to Professor D. M. Dunlop, under whose care the patients were treated, for his help and advice. Our thanks are also due to Professor G. F. Marrian for the corticoid estimations, to Dr. J. L. Potter for the measurements of capillary resistance, and to Sister E. Mutch for her invaluable assistance.

ADDENDUM.—Since this paper was written three further cases of hypopituitarism have been given A.C.T.H. Two had post-partum Simmonds's disease, and the other had had a chromophobe adenoma which had been treated surgically and with pituitary irradiation. A.C.T.H. was given in doses of 12.5 mg. every six hours by intramuscular injection. All the patients showed both subjective and objective improvement, and the only undesirable effect was slight oedema in one case.

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TUBO-UTERINE IMPLANTATION*

BY

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Practitioners and consultants alike are often confronted by a patient who gives a history of miscarriage, one pregnancy, one curettage, or one caesarean section, and yet of never again being able to conceive. Close investigation will almost invariably elicit the fact that the abortion was induced or that the pregnancy was followed by a few days of fever which quickly yielded to antibiotics or chemotherapy. When seen months or maybe years later rarely is it possible to palpate anything abnormal in the pelvis, though further study with Rubin's kymograph will show that no gas passes even at high pressures, and that the area of distension pain is low and entirely central, indicating that the blockage is at the internal ostia (Fig. 1), a conclusion even more definitely confirmed by lipiodologram.

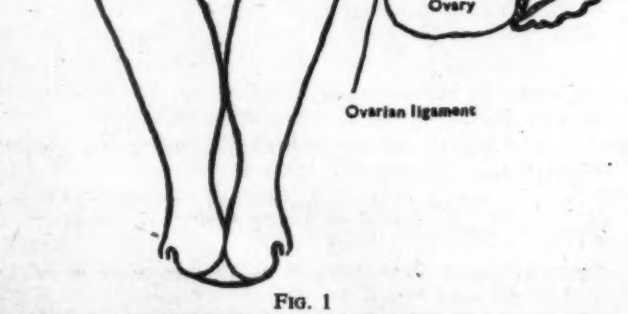

FIG. 1

* Address delivered at the All-India Surgeons' Conference in Calcutta, December, 1951.

In some parts of France and the United States of America further proof, as well as valuable information regarding the morbid anatomy of the tubes and ovaries, is thought to be obtained by culdoscopy or coelioscopy (Decker and Cherry, 1944). In this country, however, when the history is that of an induced abortion or infected pregnancy, and gas and oil investigations have been systematically carried out, it is almost invariably the rule to find at laparotomy in 82% that the isthmial and interstitial portions of the tube are alone impermeably sclerosed, whereas the distal parts of the ampullae and fimbriae are perfectly healthy (Fig. 1)—a condition almost pathognomonic of infected secundines. Very occasionally the same morbid anatomy may be present with a history of gonorrhoea, but in these cases there will always be found peritubal as well as periovarian adhesions, conditions often stultifying a good prognosis.

Implantation in the Past

Hitherto, salpingostomy or tubo-uterine implantation has raised scant enthusiasm among gynaecologists. Indeed, as Te Linde (1946) remarks, such operations are practised sometimes by some, rarely by others, and never by many. In the past, the reasons for such an attitude of mind have been (1) that the necessary apparatus for investigation of the patient before and after operation was wanting; (2) the previous history was thought too unreliable for an exploratory laparotomy; (3) the time and labour consumed were not justified by results; (4) the technical skill for a finicky plastic operation was lacking; and (5) the essential instruments were not forthcoming.

But perhaps the real death warrant lies at the door of Greenhill (1937), who, despite Solomons's (1936) questionary, sent a similar document to 107 leading American gynaecologists. Of these, 56% utterly condemned all plastic operations on the tube. The remaining 44% had, however, among them performed 818 operations, which altogether had resulted in only 54 pregnancies (6.6%), and from these only 36 live babies were born (4.4% success), for 18.5% aborted and 14.8% were ectopic pregnancies.

Such dismal results, recorded of course long before the era of antibiotics and chemotherapy, should neither depress us nor nowadays be accepted, for, as a result of much trial and careful attention to detail, the pathway is now floodlit for all to follow. Indeed, Raoul Palmer (1951), in a recent follow-up of 26 personal cases in which he had done a tubal implantation alone for the reasons specified, records eight full-term pregnancies and one ectopic, a 37.5% birth success; whereas in 18 other cases in which salpingolysis or salpingostomy was done the pregnancy success rate was only 11%. This figure corresponds with our own experience; for a fimbrial or ampullary block, with or without a hydrosalpinx, implies a pathological endosalpinx unfavourable to the passage of an ovum, whereas a clear-cut tubal implantation denotes, as a rule, a healthy mucous membrane beyond the block at the isthmus. In the 10 full-term pregnancies which Palmer records following 44 operations, caesarean section was necessary in only three. Moreover, in his latest 20 cases he has had six full-term pregnancies (30%) and no ectopics.

Such small numbers and short-term statistics are rightly looked at askance, but when they are backed by personal experience and that of many others in this country they surely challenge emulation.

Method of Tubal Implantation

Many techniques have been tried, with varying success. I advocated (Green-Armytage, 1937) the coronal uterine incision which had been advised by Bonney (see Bonney, 1947): in this the implanted tube is threaded with silkworm gut, which is brought down into the vagina. Later, ureteric catheters and stainless silver wire were employed

as tubal guides, being removed on the fifth to the eighth day through the vagina. Out of 14 such operations three pregnancies resulted—two going to term, both delivered by caesarean section, the other aborting at the fifth month.

Solomons (1927) recorded an 8.2% success rate after bisection of the uterus and leading the catgut-threaded tube through a window at the cornu into the uterine cavity. Moore-White (1951) reported two pregnancies after cornual resection using gossamer silk, and employing the usual technique when implanting ureters into the colon. Others prefer first to excise a triangular wedge from the cornu and then gently repose the patent tubal end into the somewhat large ragged hole laid bare. In one of my own cases, using this last method, the contents of the pregnant uterus herniated and ruptured at the seventh month, necessitating hysterectomy in another hospital. During the past two years I have been employing a simpler method with some success.

Before Operation

The husband and wife having been fully investigated, the date for section is fixed for a time immediately following a menstrual period; this lessens the likelihood of oozing and enhances the chances of conception at the time of ovulation five to six weeks later.

The patient is given 300 mg. of vitamin C daily for a week beforehand and a million units of penicillin daily for two days before and two days after operation.

In the theatre, under anaesthesia, a Rubin CO_2 cannula (attached to its cylinder and kymograph) is anchored to the cervix uteri. This is done for greater scientific accuracy, in that, when the abdomen is opened and the gas turned on, verification of the block at the cornu and/or the isthmus can be seen by distension and blanching. Should, however, the block be at the ampulla or fimbria, the operation of salpingolysis or salpingostomy is made easier and more satisfactory, for the bubbles can be seen rippling along the tube to explode at the external ostium—a very satisfying feature. The gas, of course, must be turned off directly the abdomen is closed, though at the end of the operation verification of patency can be repeated.

Technique

A Bonney myomectomy clamp being *in situ*, a fine probe is gently passed from the fimbrial end to the site of blockage. This is easier and quicker than distension by air, using a ball and syringe. A fine Stille forceps is applied at the block and the patent portion of the tube is cut distal to it (Fig. 2). The patent tubal end, held by delicate toothless forceps, is cut for 0.5 cm. above and below, and each flange is secured by a single knot, using silkworm-gut 5X on an eyeless needle (Fig. 2). Then, using the forceps on the isthmial blocked portion as a tractor, the myosalpinx is cut and a cylindrical tunnel the size of a pencil is cored out with a 9-mm. Silcock punch operating in the line of the interstitial portion of the tube until it reaches the uterine cavity (Fig. 3).

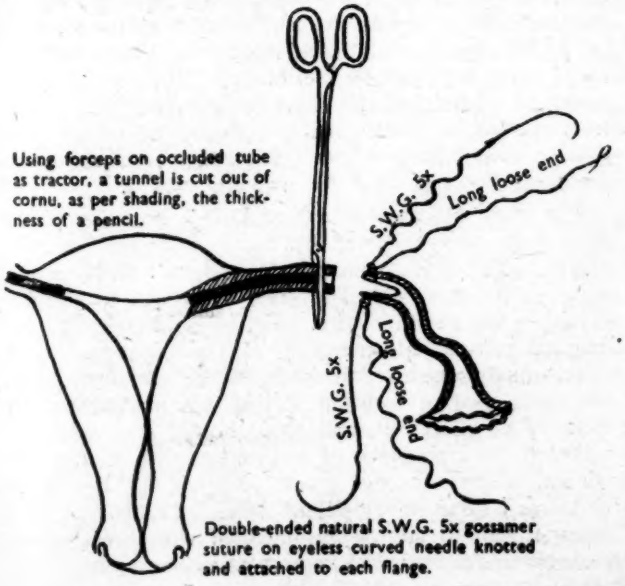
Using forceps on occluded tube as tractor, a tunnel is cut out of cornu, as per shading, the thickness of a pencil.
S.W.G. 5x
Long loose end
S.W.G. 5x
Long loose end
Double-ended natural S.W.G. 5x gossamer suture on eyeless curved needle knotted and attached to each flange.

FIG. 2

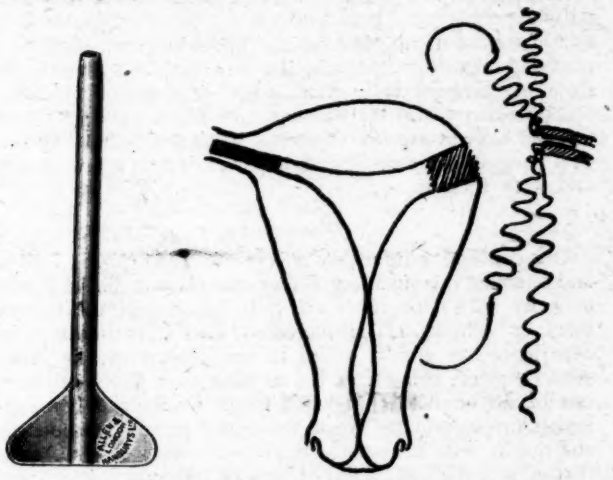

FIG. 3.—Using a Silcock punch, a tunnel the diameter of a pencil is cut at the cornu ready for implant.

At this stage a branch of the uterine artery lying between the folds of the broad ligament should be ligated lest troublesome bleeding or a haematoma occur later. Having taken great care to see that the mesentery of the tube to be implanted is conserved and its vessels are intact, the silkworm-gut needles on the two flanges are passed through the tunnel and made to emerge through the uterine wall, the one above and the other below; then, using them as reins, the tube is gently drawn through the cylindrical tunnel into the endometrial cavity. The two long loose ends depicted (Fig. 4) are then brought through the wall of the uterus, using a straight or ordinary Reverdin needle, and the two sutures secured. The external orifice of the tunnel is lightly sutured to the wall of the tube above and below (Fig. 4), great care being taken not to strangle the implanted tube in its new bed.

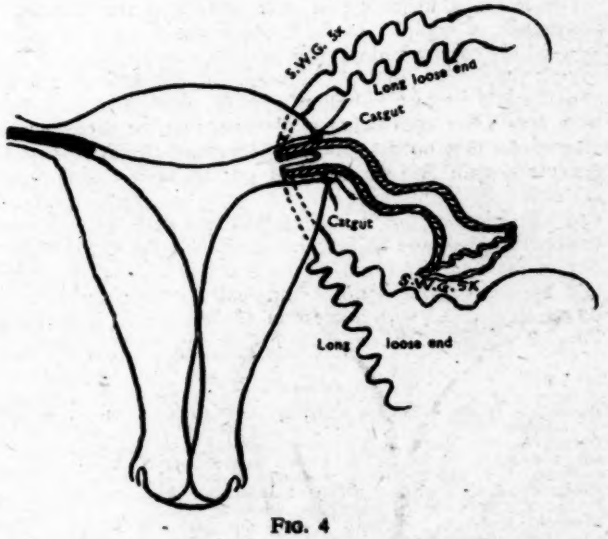

FIG. 4

The procedure is then repeated on the opposite side and the myomectomy clamp removed.

Before closing the abdomen see that the haemostasis is complete, and if necessary, using the French method of plication of the round ligaments, ventrosuspend the uterus.

The patient is put back to bed with the foot of the bed raised in order to lessen pelvic congestion. A follow-up CO_2 test is done in six to eight weeks' time. A lipiodologram is not recommended.

After using the above technique 6 patients out of 17 have conceived and gone to term. Four were confined naturally and two by caesarean section. There was one ectopic pregnancy. It is perhaps worth recording that in one of these patients, a nurse, the distal block on both sides extended almost to the ampulla and was less than 5 cm. from the fimbrial end. With an 11-mm. Silcock punch I was able to implant the wider portion of the tube with ease, the end appearance of the uterus being somewhat like that of a penguin. She conceived, however, within a few months and went to term.

Discussion

One-conception infertility is very often seen to-day. Close and scientific investigation of such cases shows that in a great majority (82%) the tubes are only blocked at the internal ostia or isthmus. The increased skill that results from experience has greatly added to our success rate in recent years—indeed, rising from 8% to more than 30%—and there can be no question that when larger numbers of gynaecologists throughout the world undertake these operations the end-results will be greatly improved and, we hope, reach that of 50% from the point of view of full-term pregnancies; for close observation and study of a number of previous failures revealed the fact, now so obvious, that it was the coning out of a jagged wedge from the cornu of the uterus with a knife that so often spelt strangulation of the tube, or later resulted in constriction by muscle scar tissue. The smooth clean-cut tunnel made by the 9 mm. modification of the Silcock punch (Fig. 3) obviates this.

Salpingostomy

As already indicated, it is a common finding that a cuff or spoon operation on the tubes, or for that matter simple salpingolysis, does not give the results one would expect, even though, in some, CO_2 tests repeated month after month are positive, with excellent oscillations.

The lessened incidence of pregnancy and the increased occurrence of ectopics in these cases would seem to point to a failure of the endosalpinx and its cilia to transmit the ovum. In others, however, although at the time of operation there is perfect bubbling rippling CO_2 patency, it has been found, on tests being made one, two, or three weeks afterwards, that no gas passes. Moreover, the area of gas-distension pain is referred right out to both iliac fossae, indicating recurrent closure at the spoon aperture or fimbrial end. To counter this it is suggested that in a suitable case the operation should be performed on the sixth to the eighth day of the cycle, and that on the first day of verified ovulation we should give a saline-and-dextrose douche and then do as Hunter did with success in 1799—namely, hornspoon into the vagina a fresh specimen of the husband's semen.

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According to the census commissioner in Delhi the population of India was 356,829,485 on March 1, 1951 (*The Times*, June 2). The ratio of females to males was 947 to 1,000. Since 1941 the population has increased by 12.5%. Over two-thirds of the population depend on agriculture for a livelihood, and nearly 83% of the people live in rural areas. Seventy-three cities have more than 100,000 inhabitants.

SULPHONE AND STREPTOMYCIN IN PULMONARY TUBERCULOSIS

BY

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Diaminodiphenylsulphone (D.D.S.) was the first sulphone to be synthesized by Fromm and Wittman (1908), but it was not until the work of Buttle *et al.* (1937) that its remarkable pharmacological and therapeutic properties in streptococcal infections in mice became known. Rist *et al.* (1940) demonstrated the action of sulphone in experimental tuberculosis in animals, and soluble derivatives—"promin" ("promanide" in Great Britain) and "diasone"—were used extensively in America and elsewhere in the treatment of animal and human tuberculosis.

Feldman *et al.* (1944) thought that D.D.S. itself was too toxic for use in man. From 1940 onwards the use of sulphones was largely confined to the soluble derivatives, promanide, diasone, and "sulphetrone," which could be tolerated in much larger doses. It was some time before it was generally realized that the efficacy of a compound was not wholly decided by the magnitude of the dose tolerated. Hinshaw and Feldman (1941) found that considerably larger doses of promanide could be given parenterally than orally without producing cyanosis. Francis and Spinks (1950) reviewed earlier work, and presented their own results, indicating that the activity of the soluble sulphones depended on the amount of free sulphone (D.D.S.) which was liberated in the body, the breakdown occurring mainly in the stomach and in the intestinal tract. The therapeutic ratio of D.D.S. proved just as good as any of its soluble derivatives.

Lowe (1950) concluded that, contrary to general belief, D.D.S. is not too toxic for use in man, and in the treatment of leprosy he established a regime of oral administration of small doses, rising from 100 to 500 mg. a day, over a period of five weeks. These small doses could be maintained for long periods, and proved at least as effective as the much larger doses of the complex soluble sulphones. Lowe (1951) now recommends a regime of 400 mg. of D.D.S. twice a week.

The small observed effects of D.D.S. on tuberculosis have been overshadowed by the discovery of streptomycin, which has a much greater demonstrable influence on the disease. The great drawback to streptomycin is the rapidity with which the tubercle bacillus acquires resistance to the drug. The possible preventive effect of sulphone administered with the streptomycin on the emergence of resistant strains was investigated by Bernard *et al.* (1950), and they showed that sulphone retarded the emergence of resistant strains, though the clinical success was not great. Francis (1952) showed that small doses of sulphone, when administered with streptomycin to guinea-pigs infected with tuberculosis, gave better results than streptomycin given alone.

Laboratory Control and Technique

In the present investigation streptomycin sensitivity was determined every two weeks; positive and negative sputa were cultured, and any growth of tubercle bacilli was tested for sensitivity by a surface diffusion method, using Loewenstein–Jensen medium. Controls of H37Rv were included in each batch of tests, and the results recorded as "sensitive," "reduced sensitivity," and "resistant." The resistant strains indicated resistance to at least 100 μg. of streptomycin per ml. Sulphone estimations were made weekly, and haemoglobin, blood counts, blood sedimentation rates, reticulocyte counts, icterus determinations, and any other examinations which were indicated were made at the same time. Sulphone (D.D.S.) estimations were made by the method of Bratton and Marshall (1939), and the extraction method of the free D.D.S. in the cases receiving the soluble 2196 followed the procedure of Francis and Spinks (1950).

The aim of the pilot trial was to determine if sulphone prevented or delayed the emergence of streptomycin-resistant strains of the tubercle bacillus, and, if a sufficient number of cases were treated, to compare the results with a similar series treated with streptomycin and P.A.S. As the M.R.C. type of case is rare in sanatoria, it was decided to use all the streptomycin-treated material.

D.D.S. was administered instead of P.A.S. in one-half of the sanatorium in every case in which streptomycin was prescribed, while continuing to use P.A.S. in the other half. In the 22 cases under test the indication for streptomycin was as follows:

Bronchial tuberculosis	6
Recent spread of disease	6
Tension cavity	4
Persistent positive sputum (collapse cases)	2
Slipping chronic	2
Tuberculous peritonitis	1
Indefinite indication	1

Plan of Treatment

At the initial conference it was decided to give 50 mg. of D.D.S. twice daily for two weeks before beginning streptomycin. From the third week 1 g. of streptomycin daily was given by intramuscular injection, and the sulphone dosage was increased to 100 mg. twice daily. After another two weeks the sulphone was increased to 100 mg. thrice daily. Streptomycin was to be given for a minimum of eight weeks, and sulphone for a minimum of 12 weeks. After the appearance of haemolytic anaemia in three of the early cases, sulphone treatment was suspended. It was then decided to administer a much smaller dose, beginning with 25 mg. daily and increasing to 50 mg. daily after two weeks. This scheme was applied to the patients already in the trial and to new entrants. Thereafter, blood changes were not alarming. Four of the 22 cases received an equivalent dosage of a soluble sulphone, "2196" (Francis and Spinks, 1950), by subcutaneous injection, instead of D.D.S.

TABLE I.—*Detailed Results*

Case No.	Sex	Age	Sputum Before Treatment	Indication	Duration of Course (Weeks)	Max. Daily Dose	Blood Sulphone Average (mg./100 ml.)	Haemoglobin		Sputum After Treatment	
								Start	Finish		
1	F	25	S	Endobronchial tuberculosis	16	Reduced 200 mg.	0·4	83 74%	70%	RS, then:	Neg. Dose reduced after 8th week. Hb drop and serious icterus
2	F	43	RS	Recent spread	14	300 mg.	0·4	92 85%	71%	R	Sulphone reduced after 7th week. Icterus and anaemia
3	F	30	RS	Endobronchial	12	200 mg.	0·15	76%	68%	R	Reduced because of drop and change of scheme
4	M	38	S	Persistent pos. sputum	12	200 mg.	0·1	82%	74%	Neg.	Sharp drop in Hb on large dosage
5	M	39	S	Recent spread	12	200 mg.	0·1	79%	71%	RS, then:	Sharp drop in R.B.C. with icterus (spherocytosis)
6	F	17	RS	Recent acute	11	200 mg.	0·35	78 69%	66%	R	Spread of disease
7	F	27	Neg.	Endobronchial	12	100 mg.	0·2	73%	72%	Neg.	Soluble sulphone
8	M	32	S	Tension cavity	13	100 mg.	0·15	93%	87%	S	
9	F	16	S	Early acute	16	50 mg.	0·35	72%	62%	R	Methaemoglobinaemia
10	F	29	Neg.	Slipping chronic	12	50 mg.	0·15	78%	73%	Neg.	Positive sputum. Not cultured after course
11	F	30	S	Recent spread	12	50 mg.	0·15	85%	75%	R	Soluble sulphone
12	M	41	S	Tension cavity	12	50 mg.	0·1	91%	80%	Neg.	Later positive. S.S. not tested
13	M	39	S	" "	12	50 mg.	0·1	91%	82%	RS, then:	Neg.
14	F	49	S	Recent spread	12	50 mg.	0·2	85%	70%	Neg.	Soluble sulphone
15	F	26	NT	Endobronchial	9	50 mg.	0·35	86%	75%	"	Sulphone stopped. Poor clinical response
16	M	22	Neg.	Slipping chronic	12	M. 2196	0·05	96%	80%	"	Sol. sulphone. Blood estimations not reliable
17	F	37	"	Tuberculous peritonitis	5	50 mg	0·3	70%	59%	"	Change to P.A.S. because of other poor results
18	F	25	S	Endobronchial	12	M. 2196	0·16	90%	78%	R	Soluble sulphone
19	F	18	NT	Endobronchial and spread	12	50 mg.	0·15	86%	73%	Neg.	" "
20	M	27	RS	Indefinite	12	M. 2196	0·25	97%	88%	R	" "
21	M	20	NT	Persistent pos. sputum	13	M. 2196	0·30	103%	93%	Neg.	Marked icterus
22	F	29	S	Tension cavities	12	50 mg.	0·3	85%	76%	R	

S = sensitive. RS = reduced sensitivity. R = resistant. NT = not tested.

Results

The detailed results are shown in Table I. In 15 out of the 22 cases the organism was isolated from the sputum and tested for streptomycin sensitivity before treatment was started. Eleven strains were fully sensitive, and four showed some reduction in sensitivity; none were resistant. The remaining seven cases were either negative at the time or an organism seen on direct smear failed to grow on culture, and therefore could not be tested for sensitivity. Twelve strains were isolated either during treatment or after its completion. Of these, one was fully sensitive, three showed reduced sensitivity before disappearing from the sputum, and eight were completely resistant to streptomycin. The fate of the strains is shown in Table II.

TABLE II

Before Treatment	After Treatment
11 Sensitive	1 Sensitive 3 Reduced sensitivity (negative later) 4 Resistant 3 Negative
4 Reduced sensitivity	4 Resistant
7 Negative	7 Negative

Because of the rapid emergence of resistant strains the trial was stopped after it had been made in 22 cases. This small number does not lend itself to analysis of the therapeutic effectiveness of the streptomycin–sulphone combination, but the results were not encouraging. Streptomycin

and P.A.S. gave very good results in a large number of cases of endobronchial tuberculosis. The six cases of this condition treated with streptomycin and sulphone, however, produced only one satisfactory result; two showed considerable improvement and two slight improvement; and one patient, whose strain showed reduced sensitivity before treatment, was unimproved.

Complications.—The only serious complication encountered was haemolytic anaemia, which was present in three of the six patients who received a daily dose of 200 mg. or more of D.D.S. One of these showed a drop of over two million red cells per c.mm. in a fortnight. After a short interval (two weeks) treatment was resumed on the reduced dosage scheme, and the haemoglobin slowly improved. In spite of iron administration throughout there was an average drop of 10% haemoglobin in the 22 patients. Methaemalbumin was present in the blood in three of the high-dosage cases, and the violet coloration of the skin associated with this substance was observed in two further cases.

Discussion

The African leper and the European tuberculous patient appear to differ greatly in their tolerance to sulphone. Lowe's cases (Lowe, 1950) received up to 300 mg. of D.D.S. a day, giving blood levels from 0.8 to 1.4 mg. per 100 ml. without showing haemolysis, whereas a smaller dosage scheme in our cases caused severe haemolysis with a much lower blood sulphone level of from 0.2 to 0.6 mg. per 100 ml. It certainly seemed inadvisable to proceed with our original dosage scheme, which was based on the leprosy work, when serious drops in erythrocyte counts occurred with great rapidity.

There is no apparent trend suggesting a correlation between blood sulphone levels and emergence of resistant strains. The only surviving sensitive strain was in a patient whose blood sulphone never exceeded 0.15 mg. per 100 ml.

The emergence of eight resistant strains and only one fully sensitive strain after eight weeks' streptomycin treatment compares very unfavourably with the findings in the streptomycin and P.A.S. group of the M.R.C. (1950) trial, in which 97% showed a resistance ratio of less than 9 at the same stage of treatment. Bernard *et al.* (1950) found 51% resistant strains after 70 days of combined streptomycin and sulphone treatment, compared with 91% in the control group treated with streptomycin alone. This result also is much worse than the M.R.C. streptomycin and P.A.S. group.

Conclusions

D.D.S. is not tolerated in doses of 200 mg. daily by European tuberculous patients.

In the tolerated dosage it does not prevent or delay the emergence of streptomycin-resistant strains of *Myco. tuberculosis.*

The clinical results with combined streptomycin and D.D.S. were not encouraging.

Our thanks are due to Messrs. I.C.I. (Pharmaceuticals) Limited for the supply of D.D.S., and to Drs. L. B. Wevill and A. S. R. Stewart and Professor J. Francis, with whose collaboration the trial was planned, for their invaluable criticism and advice.

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MEGALOBLASTIC ANAEMIA OF INFANCY

BY

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Megaloblastic anaemia of infancy was first recognized as a distinct clinical syndrome by Zuelzer and Ogden (1946). The disease occurs predominantly within the first year of life, is characterized by a fairly distinctive clinical pattern, and responds to folic-acid therapy. The response to folic acid is often complete and permanent. Since its original description the disease has often been reported from America, though the only case recorded by British authors is that by Hutchison and MacArthur (1949). A further case is here described and the literature on the subject is briefly reviewed.

Case History

A baby girl aged 8 months was referred by her practitioner for a blood count on August 8, 1951. She was the youngest of a family of three children, her sister and brother being healthy and never having suffered from anaemia. The mother is in good health and has never suffered from anaemia either before or during her recent pregnancy. For the first three months of life the child had been breast-fed, and during this time she was well and there were no feeding difficulties. After the third month she was weaned and put on National dried milk, her diet being supplemented by daily orange juice and cod-liver oil. After about one month on dried milk she first started to show symptoms of feeding difficulty characterized by frequent attacks of diarrhoea and vomiting coupled with a marked reluctance to take her feeds. During the three months before admission increasing pallor had become evident.

Clinical examination revealed a very pale infant weighing 15 lb. (6.8 kg.)—about 3 lb. (1.4 kg.) under her expected weight—with a temperature of 99° F. (37.2° C.), but no other physical abnormality. A blood count at this time showed: Hb, 46% (6.8 g. per 100 ml.); red cells, 1,900,000 per c.mm.; reticulocytes, 0.8%; white cells, 16,000 per c.mm.; the differential count showed one nucleated red cell for every 100 white cells counted, and 63% lymphocytes.

The infant was admitted to hospital during the course of the next few days. A blood count on admission showed little change except for one important feature: nucleated red cells were still present, and a few of these showed a quite distinctive megaloblastic pattern. A diagnosis of megaloblastic anaemia of infancy was suggested on this finding and a tibial puncture was performed. The marrow showed a typical megaloblastic reaction. Not only were the erythroblasts of megaloblastic type, but hypersegmentation of polymorphs and ballooning of metamyelocytes were evident.

Other investigations included a fractional test meal, which showed free acid after histamine stimulation. The faeces were examined for evidence of steatorrhoea, but analysis revealed normal fat content. Tests for occult blood were negative, and no parasites were found in the faeces. The Wassermann reaction and Coombs test were negative. Radiographs of the long bones showed no abnormal features.

Treatment consisted of only one 10-mg. dose of folic acid and one 10-μg. dose of vitamin B_{12}. Within a very short time there was a dramatic clinical and haematological response. On the fifth day the reticulocyte count reached a peak of 26%. The haemoglobin showed a steady rise, and 15 days after treatment it had risen from 46% to 84%. Within 36 hours of treatment bone-marrow films showed a complete reversion to normoblastic erythropoiesis. Marrow

smears obtained 11 days after the starting of treatment again showed a normoblastic pattern. The clinical improvement was steadily maintained and the patient was discharged from hospital three and a half weeks after admission. Five months after discharge she relapsed. A blood count on readmission showed: Hb, 44% (6.5 g.); red cells, 2,400,000 per c.mm.; white cells, 6,000 per c.mm. Folic acid was administered and again dramatically converted the blood picture to normal. Since discharge the patient has been kept on a daily maintenance dose of 10 mg. of folic acid. She has remained well and her blood picture is normal in every way.

Discussion

Megaloblastic anaemia of infancy was first recognized by Zuelzer and Ogden in 1946, although Amato (1946) in the same year described several cases in Italian infants. Zuelzer and Ogden originally described 25 cases of the disease occurring in infants under 18 months of age. In their series of cases the outstanding clinical feature was extreme pallor. They described the disease as having an insidious onset, usually associated with symptoms of upper respiratory or gastro-intestinal infection. Of their 25 cases 6 showed evidence of clinical scurvy. All the infants responded well to treatment with pteroylglutamic acid (folic acid).

Since the above original report many other cases have been recorded (Aldrich and Nelson, 1947; Siebenthal, 1948; Hutchison and MacArthur, 1949; Luhby and Wheeler, 1949; Woodruff *et al.*, 1949; Taylor and Hettig, 1949; McPherson *et al.*, 1949; Sturgeon and Carpenter, 1950). The cases reported by these authors have served to confirm the clinical and pathological features originally described by Zuelzer and Ogden.

Reisner *et al.* (1951) have described four new cases of a megaloblastic anaemia in infants which they term "juvenile pernicious anaemia." The existence of pernicious anaemia in children is largely doubted, though several cases have been reported as true pernicious anaemia (Faber, 1928; Bachman, 1936; Langmead and Doniach, 1937; Davis, 1944; Petersen and Dunn, 1946). The last-named authors laid down the criteria for the diagnosis of pernicious anaemia in the following terms: the anaemia should be macrocytic; histamine-fast achlorhydria should be present; the marrow should show megaloblastic erythropoiesis; the anaemia should respond to liver therapy; and continuous treatment should be necessary to maintain a continued remission.

If these criteria be accepted, almost all of the previously reported cases of juvenile pernicious anaemia become unacceptable. In one case only, that described by Peterson and Dunn, does there seem to be any justification for naming the disease juvenile pernicious anaemia, and even in this case it may well be argued that enough time has not yet elapsed to satisfy the last requirement. It is not yet known whether these cases will need liver therapy into adult life.

Reisner *et al.* have gone even further, and have separated juvenile pernicious anaemia from megaloblastic anaemia of infancy on the response to vitamin B_{12}. Those children relapsing after vitamin-B_{12} therapy are regarded as cases of juvenile pernicious anaemia, while those responding to it and not needing maintenance therapy are classified as megaloblastic anaemia of infancy. This classification has been adopted notwithstanding the fact that most cases of megaloblastic anaemia of infancy do not respond satisfactorily to vitamin-B_{12} therapy. Moreover, of the four cases reported by Reisner and his associates three had free acid in the gastric juice. The very term pernicious anaemia has long since lost its descriptive value, and it is clearly wrong to extend the term to embrace other types of megaloblastic anaemia. The presence of a histamine-fast achlorhydria should be regarded as a *sine qua non* before a diagnosis of pernicious anaemia is established.

Aetiology

In view of the frequently reported association of scurvy in megaloblastic anaemia of infancy May *et al.* (1950) placed monkeys on various diets which resembled those reported for different infants who have developed the anaemia. The animals used were of a species known to be susceptible to vitamin-C deficiency and also capable of developing megaloblastic anaemia. The monkeys varied in age from newly born to nearly mature. Each diet was fed to the animals with or without vitamin C. The results were remarkable in that no monkey given vitamin C developed the anaemia and all monkeys deprived of ascorbic acid regularly developed megaloblastic anaemia. Administration of pteroylglutamic acid was promptly effective in relieving the anaemia. Ascorbic acid was also effective, but took much longer to cure the disease, whilst vitamin B_{12} was without effect unless given in conjunction with ascorbic acid, when it produced prompt relief. It has been suggested that ascorbic acid does not have a direct haemopoietic effect but acts by sparing folic acid. Luhby and Wheeler (1949) regard the disease as essentially a folic-acid-deficiency state.

The possibility of maternal deficiency in folic acid has received some support since Jones and Smith (1950) demonstrated that pteroylglutamic acid could cross the placenta of the pregnant rat and affect embryonic haemopoiesis. This finding may well have some bearing on the aetiology of the disease.

Although folic acid is the drug of choice in the treatment of megaloblastic anaemia of infancy, McPherson *et al.* (1949) and Sturgeon and Carpenter (1950) have reported good results following the administration of vitamin B_{12}. Several cases, however, have shown little or no response to vitamin B_{12}.

It seems not unlikely that folic-acid deficiency is the most important factor predisposing to the development of the anaemia, but that ascorbic acid and vitamin B_{12} are also important and may affect the degree of folic-acid deficiency.

Summary

A case of megaloblastic anaemia of infancy is described.

There was a dramatic response to folic-acid therapy.

Other cases of megaloblastic anaemia of infancy and so-called juvenile pernicious anaemia are briefly reviewed.

It is suggested that the term juvenile pernicious anaemia should not be used in describing megaloblastic anaemias in infancy and childhood.

I wish to thank Dr. E. A. J Byrne, consultant paediatrician, under whose care the patient was admitted, and Dr. M. C. G. Israëls for his helpful comments.

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TUBERCULOSIS IN MENTAL HOSPITALS*

BY

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In Great Britain the special problem which tuberculosis constitutes in mental hospitals has never been accorded the attention it merits. This is well illustrated by reviewing the bibliography on this subject in the world medical literature. Here one finds that of over thirty papers on this subject only a few (Snell *et al.*, 1943; Clark *et al.*, 1945; Early, 1950) have been published by workers in the United Kingdom; and the overwhelming bulk of contributions have been by United States and Canadian investigators. In the latter countries great interest has been evinced, and a most vigorous policy pursued in combating tuberculosis in this field, by the Federal Public Health Agency (*Public Health Reports, Wash.*, 1949), by State and mental hospitals, and by a variety of subcommittees (Committee on Tuberculosis in Mental Hospitals, 1946) concerned in the prevention of tuberculosis. In Great Britain an attitude of casualness bordering on indifference has arisen. Our first task, therefore, must be to find out whether tuberculosis really does constitute a problem in mental hospitals. The following evidence, culled from the publications of the Board of Control (1949), is submitted.

The Board of Control returns for 1949 show that there were 650 notifications of tuberculosis and 300 deaths from tuberculosis per 100,000 mental hospital patients. In 1948 there were 384 male and 190 female deaths among mental hospital patients (Board of Control, personal communication). Moreover, during 1948 approximately one out of every ten deaths occurring in male mental hospital patients was due to tuberculosis. While the above facts give some ground for concern, the most striking evidence of the gravity of this problem is illustrated by an analysis of the death rate in mental hospitals. Whereas 2.8% of the national deaths due to tuberculosis occur in mental hospitals, this community constitutes only 0.35% of the population of England and Wales.

Present Survey

In order to obtain more precise information about this problem a survey was conducted during 1950 in a large mental hospital in Yorkshire. Details of the sex and age distribution of this population are outlined in Table I. It

TABLE I.—*Mental Hospital Population in Age Groups*

Age	Females		Males	
	No.	%	No.	%
Under 20 years ..	12	0·74	10	0·83
20 to 39 ,, ..	260	16·1	304	25·3
40 ,, 59 ,, ..	671	41·6	495	41·0
60 and over ..	669	41·5	390	32·5
	1,612		1,199	

will be observed that a very large proportion of the population are 40 years or over; therefore such conclusions as emerge from this survey are not necessarily representative of mental hospitals throughout the country as a whole, though they may be helpful in indicating the pattern and possibly the magnitude of this problem.

Inquiry into the literature revealed that it would have been valueless to attempt to assess the tuberculin reactor rate of the population to patch or jelly tests. Leonidoff (1943), working on this problem in the United States, found that about one-sixth of such tests were damaged or removed by patients. It was therefore decided to inject intradermally all patients, apart from those known to be suffering from pulmonary tuberculosis, with a single dose of 1:100 old tuberculin.

The distribution of tuberculin reactors according to age, sex, and duration of residence in the mental hospital is outlined in Tables II and III.

TABLE II

Age	Percentage of Tuberculin Reactors in Mental Hospital	
	Females	Males
Under 20 years	—	—
20 to 39 ,, ...	89·6	95·7
40 ,, 59 ,, ...	91·3	95·0
60 and over	91·2	96·9
Overall Percentage of Tuberculin Reactors	89·95	96·5

TABLE III

Duration of Residence in Mental Hospital	Percentage of Tuberculin Reactors in Mental Hospital	
	Females	Males
Under 3 months	85·0	91·5
3 to 24 ,, ...	88·5	95·3
25 ,, 60 ,, ...	91·5	95·85
Over 60 ,, ...	91·4	96·1
Overall Percentage of Tuberculin Reactors	89·95	96·5

A number of interesting points emerged in the analysis of the above findings. First, there appeared to be no obvious difference in the reactor rate as between different mental diseases when classified according to the psychiatrist of the hospital. Secondly, when mental patients were classified according to the duration of their stay in mental hospitals, it would appear that males with less than three months' residence had a significantly higher percentage of *negative* tuberculin reactors. This does suggest that new admissions may have about the same exposure incidence to active pulmonary tuberculosis as the mentally normal civilian population, but that the reactor rate rose appreciably after three months' residence, probably because of the greater number of open male cases of tuberculosis in this mental hospital. This observation tends to support Oechsli's (1949) findings that of patients resident under six months the incidence of active tuberculosis is 1.6%, those resident under five years 3%, and those resident over five years 8.8%. Thirdly, it appeared that the reactor rate among females was always lower than among male patients.

The original intention was to take *x*-ray films of the entire mental hospital population. Unfortunately, owing to technical difficulties, this survey could be completed in the male wards only. Of the 1,199 male patients who underwent mass radiography no fewer than 67 (13 previously known and confirmed) were found with radiological evidence of pulmonary tuberculous lesions which were neither wholly calcified nor fibrotic. Among the 54 newly discovered cases with radiological lesions, 25 were designated as active (positive sputum or cavitation) and 29 as pulmonary tuberculosis of "undetermined activity."

Clinical examinations appeared to be an unusually fruitless field in the assessment of lung activity in mental patients. The schizophrenics were often very shallow breathers, and many of the low-grade mental defectives simply did not respire normally and were uncooperative with a strange

*Substance of a paper read at a joint meeting of the Royal Medical Psychological Association and the National Association for the Prevention of Tuberculosis held on November 15, 1951.

physician. The only further investigations attempted in this survey were the sedimentation rate, two laryngeal swabs, and faeces examinations for tubercle bacilli in each of the 67 cases with pulmonary tubercle of active, quiescent, or undetermined activity (Table IV).

TABLE IV.—*Results of X-ray Examination of Male Mental Hospital Population in 1950*

Total No. of males *x*-rayed	1,199	
Newly detected:		
Patients with positive sputum	12	54 (4·5%)
Patients with radiological evidence of cavitation	13	
Patients with radiological tuberculosis of undetermined activity	29	
Previously detected and confirmed:		
Patients with active and quiescent pulmonary tuberculosis	13 (1·1%)	
Total with pulmonary tuberculosis of active, quiescent, and undetermined activity	67 (5·6%)	

Another interesting finding which emerged in the course of investigation was that this mental hospital had a sanatorium ward in the male wing for the isolation of 58 tuberculous patients. Radiological evidence of active or quiescent tuberculous disease was not revealed in 43 patients. The bulk of the latter were found to have healed pulmonary tuberculosis, bronchiectasis, chronic bronchitis with emphysema, and asthma. Only 13 of the inmates revealed evidence of active or quiescent lung tuberculosis; a further two patients suffered from intestinal tuberculosis. This experience is similar to that of Snell *et al.* (1943), who found that 19 of 48 notified cases of pulmonary tuberculosis in mental hospitals showed either healed lesions or no evidence of pulmonary tuberculosis.

A few general comments and clinical findings may be of value. It was remarkable to note the paucity of signs and symptoms in five mental patients with extensive bilateral disease with cavitation. Another surprising observation, revealed on inspection of the chest skiagrams, was the extensive lung scarring and calcification which had occurred in the absence of any special medical treatment. Whether the ordered mental hospital regime was a factor in aiding the patient's natural powers of healing is an interesting speculation.

Discussion

Problem of the Mental Hospital Patient.—In the overwhelming bulk of mental patients suffering from tuberculosis precedence must be directed to the treatment of the *mental disorder* of the patient. Next in importance, attention has to be focused on the prevention of the spread of tuberculosis from the infected to the non-infected mental patient, from the infected patient to the non-infected mental nurse, and from the infected patient to the mentally healthy community. Thirdly, tuberculosis therapy in the tuberculous mental patient has only limited application at the moment, and therefore ought not to command the same emphasis as the two other measures in coping with this problem.

Problem for the Community.—Only a minority of physicians have realized the profound transformation which has occurred in the therapeutic scene in psychiatry in the past two decades. At present, more than a quarter of the mental hospital inmates are discharged home annually, and this group may contain up to 200 patients suffering from pulmonary tuberculosis. Tuberculosis in the mental patient is therefore no longer simply a problem of the mental hospital, but has assumed epidemiological dangers for the community. Therefore it is important that there should be the closest liaison between the medical superintendent of the mental institution and the medical officer of health, so that the latter can be informed some weeks before a patient's discharge and arrangements made for separate accommodation and extra nourishment for the mental patient, the provision of a home help, B.C.G. vaccination of his contacts, etc.

Problem for the Mental Nursing Staff.—In the past, mental nursing staffs have received limited instruction in tuberculosis in the course of their training. Tuberculosis seems to be but one of a number of subjects in the nursing syllabus covered by the broad term "general medicine." It would be a wise gesture if chest physicians were encouraged to give instruction on the hazards and prophylaxis of tuberculosis in mental hospitals.

In future, nursing staffs will be tuberculin-tested, B.C.G.-vaccinated, and periodically *x*-rayed along the lines recommended for the nursing profession in a recent Ministry circular. However, there seems to be an even greater need for safeguarding the health of nursing staff in mental hospitals than in sanatoria. In the latter institutions nurses are constantly on their guard against the hazards of infection. Sanatorium patients are educated on admission in simple hygienic measures like screening their mouth with the hand on coughing, yawning, and expectorating. In the general wards, especially in the admission block of the mental hospital, the nursing staff may not be quite as vigilant or aware of these dangers of infection, and, moreover, a considerable number of patients cannot be educated to control indiscriminate coughing. It would therefore be reasonable to require as high a standard of hygiene discipline from mental hospital nurses as that prevailing in sanatoria. Gowns and masks should be worn while wards are being swept and beds made. That these precautionary measures are necessary can be seen from examination of the findings of Katz *et al.* (1945), Deegan *et al.* (1942), Altshuler *et al.* (1941), and Burns *et al.* (1936), who discovered that among their nursing personnel 1.1%, 1.5%, 3.5%, and 3.7% respectively suffered from pulmonary tuberculosis.

Conclusion

By the adoption of the above measures, designed to limit tuberculosis in mental patients and its spread to mental nursing staffs and the outside community, we can hope to liquidate one of the principal foci of tuberculous infection which still remains in this country.

I wish to record my thanks and appreciation to Dr. Bruce, consultant psychiatrist; Dr. F. Ridehalgh; Dr. S. Keidan, acting medical director, Leeds Mass Radiography Unit; Mr. Woodcock, chief male nurse; and Nurses Cranston and Nichol; also to Miss F. Stephen for her invaluable secretarial assistance.

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At a recent meeting organized by the British Gelatine and Glue Research Association, Dr. John T. Edsall (Professor of Biological Chemistry, Harvard) discussed the process of blood clotting, which can be considered broadly as occurring in two stages, the first involving the complex series of processes whereby prothrombin is converted to thrombin, and the second the action of thrombin on fibrinogen to form the fibrin clot. The major constituent in the second stage is fibrinogen; it seems quite clear that thrombin acts catalytically. The size and shape of the fibrinogen molecules have now been studied by many methods—sedimentation and diffusion, viscosity, osmotic pressure, double refraction of flow, electron microscopy—and they appear to be rod-shaped, each about 700A by 40A, with a molecular weight of the order of 450,000. Recent work indicates the splitting off of a small peptide from fibrinogen by the action of thrombin, with the formation of free terminal α-amino groups of glycine residues in fibrin. The subsequent process of polymerization involves both end-to-end and side-by-side aggregation, the latter becoming relatively less important as the *p*H increases.

Medical Memoranda

Progressive Bacterial Synergic Gangrene of the Legs

Bacterial synergic gangrene is a comparatively rare disease. It usually occurs after abdominal operations, and as a result is commonly known as post-operative progressive bacterial synergic gangrene. The infection is essentially confined to the skin, which characteristically is not totally destroyed: islets of epithelium escape complete destruction. Gangrene often starts in the skin around retention sutures, following drainage of an intraperitoneal abscess or an empyema. Sometimes it develops slowly around a colostomy, an ileostomy, or a suprapubic fistula. Rarely it may follow trivial superficial abrasions or skin lesions on the limbs.

The aetiology of the condition was first clearly demonstrated by Meleney (Brewer and Meleney, 1926). It is due to the synergic action of a micro-aerophilic non-haemolytic streptococcus and a haemolytic *Staphylococcus aureus*. The organisms are nearly always found far out in the spreading edge of the lesion. Other organisms, such as *Pseudomonas pyocyanea, Bact. coli, Proteus vulgaris, Streptococcus faecalis,* diphtheroids, and non-pathogenic staphylococci, may occur as secondary invaders in the gangrenous skin. Any of these may overgrow the original infecting organisms and render it impossible to isolate them unless cultures are carefully made from the spreading edge of the lesion. The synergic nature of the infection has been confirmed by Lyall and Stuart (1948). From animal experiments these authors present evidence that *P. vulgaris,* combined with the micro-aerophilic streptococcus, occasionally produces the lesion, but that the individual organism fails to do so.

The clinical picture is characteristic. The chief symptom is severe pain and marked tenderness at the edge of the ulcerated area. There is an outer non-tender zone of erythema ranging from 1 to 10 cm. in width. It blends on its inner side with a raised, purple, sharply defined, vesiculated zone. The latter is firmly adherent to the gangrenous skin, which has a suède-leather appearance, and varies from 1 to 10 cm. in width. The gangrenous skin is at first only slightly undermined, but gradually it melts away, leaving an unhealthy granulating area. On occasion, healing occurs in the centre while the margin extends like ringworm in all directions.

Until 1945 the treatment was wide diathermy excision of the lesion followed by skin grafts. This was not always satisfactory and had to be repeated so as to get well beyond the spreading margin. In some cases zinc peroxide, applied locally after surgical excision, arrested the lesion (Meleney *et al.*, 1945). In general the treatment was not satisfactory and death followed from extension of the lesion.

Owing to the unsatisfactory results from surgical treatment, trials of penicillin were made by various investigators. Reports of successful treatment with penicillin soon appeared in the literature (Meleney *et al.*, 1945; Grimshaw and Stent, 1945; Canton, 1945, 1946; Cedarblade and Orr, 1946; Clarke, 1947). In successful cases the inflammation, induration, oedema, and pain around the wound resolved and healing occurred rapidly, skin grafts sometimes being unnecessary. Not all cases of bacterial synergic gangrene responded to penicillin. These cases had either penicillin-resistant organisms or were contaminated with secondary invaders which actively produced a penicillinase which destroyed penicillin. Favourable results have been obtained from the parenteral administration of bacitracin in these penicillin-resistant cases. The effect of this newer antibiotic is dramatic, and five typical cases healed promptly (Meleney *et al.*, 1950). The report of a case of bacterial synergic gangrene of the legs treated with other antibiotics followed by limited surgery may be of interest.

CASE REPORT

The patient, a man aged 76, sustained multiple injuries and a puncture wound on the left shin on June 10, 1950. Penicillin, 500,000 units six-hourly, was given. On June 22 large blisters appeared on both legs. Penicillin was discontinued, and "sulphatriad," 1 g. six-hourly, was given. A fluctuant area on the lateral aspect of the right knee was noticed on June 29. The area was incised and the serous discharge released. Streptomycin, 1 g. daily, was given and the sulphatriad discontinued. On August 22 the gangrenous process extended up both thighs (see illustration).

Gangrenous process. Condition on August 22.

Chloramphenicol 500 mg. eight-hourly (total 9 g.), penicillin 200,000 units twice daily, sulphatriad 0.5 g. six-hourly, and streptomycin 0.5 g. six-hourly were given. On August 30 the chloramphenicol was increased to 750 mg. six-hourly (total 18 g.). Next day the patient was much improved. On September 8 the spreading margin was arrested and the course of chloramphenicol was completed.

Operation.—Right thigh: A linear diathermy incision was made 2–2½ in. (5–6.3 cm.) above the spreading margin. Left thigh: A cuff of skin 1¾–2 in. (4.4–5 cm.) wide was excised 3 in. (7.6 cm.) above the spreading margin. On September 19 all the gangrenous skin separated completely up to the diathermy incision, but three small areas were infected in the upper flap on the left side.

A diathermy incision was made 2 in. (5 cm.) beyond the infected areas in the upper flap. On October 3 the infection in the thigh completely resolved and healing was progressing rapidly.

COMMENT

It was not possible to establish the presence of the micro-aerophilic streptococcus, although repeated aerobic and anaerobic cultures were made from the spreading margin. The clinical appearance and progress of the case, however, conformed to those of bacterial synergic gangrene.

The remarkable feature of this case was the rapid growth of fresh epithelium once the sloughs had separated. Of all the antibiotics used in the treatment, only chloramphenicol produced improvement in the local and general condition of the patient. It slowed down the rate of spread of the infection and in some areas completely eradicated it.

My grateful thanks are due to Professor Charles Wells and Mr. Norman Roberts, who entrusted me with the care of this

patient. I also thank Professor A. W. Downie and Dr. T. Black for the bacteriological investigations and sensitivity tests. The chloramphenicol was supplied by the Medical Research Council.

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Fatal Staphylococcal Septicaemia Following Removal of Tonsils and Adenoids

From the most recent report of the Chief Medical Officer of the Ministry of Education it is evident that at least 1,500 children are operated on each week in this country for the removal of their tonsils and adenoids. The case we record below must fortunately be a rare occurrence, as a search of the literature has failed to reveal any report of a fatal staphylococcal septicaemia following this operation, particularly when it is carried out under an umbrella of penicillin.

CASE REPORT

A girl aged 13 was admitted to hospital for removal of tonsils and adenoids on December 20, 1951. Her previous history was that when she was 4 years old glands on the left side of the neck had discharged spontaneously; these were diagnosed as tuberculous. At the age of 5 she had rheumatic fever. She had also had measles, whooping-cough, and chicken-pox. On examination she was seen to be a pale girl, tall for her age. The tonsils were enlarged, one tooth was septic, and slight nasal discharge was present. Mitral stenosis was diagnosed, but no active disease of the heart was found.

On admission she was placed on 1 ml. of "distaquaine penicillin" twice daily, on account of her heart condition, and this was continued for eight days after operation. The operation was performed successfully on December 21. Convalescence was uneventful until the eighth day, when secondary haemorrhage from the adenoid bed occurred. The haemorrhage, however, stopped spontaneously; she was given a further 1 ml. of distaquaine penicillin on December 30 and 31, and was discharged on January 2, 1952, 13 days after her operation, apparently fit and well.

On January 4 she woke up with severe frontal headache and fleeting joint pains which progressively increased. She was seen by her family doctor, who gave her daily injections of penicillin on January 5, 6, and 7. Her condition deteriorated, and she was readmitted to hospital on the 10th. On admission her temperature was 104.6° F. (40.3° C.), pulse 144, and respirations 28. Neck rigidity was marked, and she was semi-comatose. A petechial rash was present on the trunk and extremities. She had suffused conjunctivae, but her fauces appeared clean and healed. *X*-ray examination of skull, chest, and cervical and thoracic spine revealed no abnormality. A white-cell count numbered 26,000 per c.mm. (polymorphs 83.5%, eosinophils 0.5%, plasma cells 2%, metamyelocytes 6%, myelocytes 1.5%, monocytes 1.5%, lymphocytes 5%). The cerebrospinal fluid showed: cells, 235 per c.mm. (polymorphs 80%, mononuclears 20%); Gram-stained film, no organisms seen; sugar, 45 mg. per 100 ml.; chlorides, 620 mg. per 100 ml.; protein, 70 mg. per 100 ml.; culture yielded no growth in 48 hours.

Her general condition was very poor, and on the same day she was transferred to an infectious diseases hospital with a tentative diagnosis of an incompletely treated coccal meningitis. She was immediately given 2,000,000 units of crystalline penicillin intramuscularly, 1 g. of "soluthiazole" intravenously, and 5 mg. of "percorten" (deoxycortone acetate) intramuscularly, followed by three further intramuscular injections of 2,000,000 units of crystalline penicillin at four-hourly intervals. Another 2 g. of soluthiazole and 5 mg. of percorten were also given, but she died on January 11, within 24 hours of admission to hospital.

FINDINGS AT NECROPSY

Post-mortem examination on the following day showed multiple petechiae on the extensor and flexor surfaces of both arms and legs; one of these petechiae was removed for sectioning. Within the substance of the cerebellum there was a blood clot measuring 2 in. (5 cm.) in diameter. In the cerebrum there was an abscess ½ in. (1.27 cm.) in diameter in the region of the right insula. Sphenoidal, frontal, and ethmoid air sinuses appeared normal. So far as could be seen the mouth, tongue, fauces, pharynx, and nasopharynx were clear. The pleurae were normal and the lungs moderately congested, with no macroscopic abscesses. The heart showed mitral stenosis. Macroscopically, the endocardium and myocardium were normal. No vegetations were found on any of the heart valves. There were enlarged mesenteric and coeliac glands and a small quantity of clear fluid in the peritoneal cavity. No peritonitis was seen. The liver had two small septic infarcts on the superior surface of the right lobe, otherwise it was normal. The spleen was grossly enlarged—weight 18¼ oz. (523 g.)—and on cutting was "toxic-looking" and contained two septic infarcts. There was a septic infarct in the upper pole of the right kidney. The suprarenal glands appeared normal—an observation confirmed by subsequent histological examination. No other abnormality was found in the abdominal cavity.

A blood culture had been taken while the patient was alive, and this grew a coagulase-positive mannite-fermenting *Staphylococcus aureus*. Swabs taken *post mortem* from the septic infarcts as well as from the pharynx and trachea all grew a similar *Staph. aureus*. All the staphylococci isolated were resistant to penicillin (10 units per ml.) and "sulphatriad" (10 mg. and 100 mg. per ml.), but sensitive to streptomycin (10 mg. per ml.) and chloramphenicol (25 μg. per ml.). Staphylococci from the sites mentioned in the Table were sent for phage-typing, and all proved to be of the same type.

Site	Organism	Coagulase	Mannite	Phage Pattern
Blood culture ..	*Staph. aureus*	+ve	+	47/53+
Nasopharynx ..	" "	"	+	47+
Trachea	" "	"	+	47/53+
Brain	" "	"	+	47/53+
Pelvic peritoneum	" "	"	+	47/53+
Spleen	" "	"	+	47/53+

Sections taken for histology from abscess areas, including the skin lesion, all showed large numbers of Gram-positive cocci. The lung sections showed congestion, but no microscopical abscesses were seen. Histologically, the section of the cerebellum showed only a blood clot and normal cerebellar tissue. We assume that the immediate cause of death in this case was cerebellar haemorrhage, probably due to a septic infarct eroding one of its vessels.

COMMENT

No definite primary focus of infection could be identified at the post-mortem examination. It appears, however, a reasonable presumption that the *Staph. aureus* isolated in this case from various sources having the same phage pattern was introduced through the raw surface of the adenoid bed, since a secondary haemorrhage which occurred from it on the eighth post-operative day was almost certainly due to infection.

Our thanks are due to Dr. R. E. O. Williams for phage-typing and to Dr. T. V. Cooper for his advice in the preparation of this paper.

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O. G. JONES, M.R.C.S., L.R.C.P., D.C.P.

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The Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education for the years 1948 and 1949, Chapter VI, p. 41.

Acute Suppurative Parotitis in the Newborn

As reports of this condition are few in number the following case is thought to be worth recording.

CASE REPORT

On October 11 a primigravida was delivered of a female infant which suffered from a severe degree of "white asphyxia." Attempts at breathing amounted merely to an occasional gasp, and lobeline, nikethamide, aspiration of mucus from the pharynx, nasal oxygen, immersion in warm water, and, finally, mouth-to-mouth inflation through an ordinary double-layer face-mask were all employed. Normal respiration was established after 75 minutes. During the first five days of life the baby remained restless, and was spoon-fed with difficulty. She eventually settled down, but the fluid intake was barely sufficient, and oesophageal tube-feeding was employed from the seventh to the tenth day, when sucking was established. At this time, October 20, the right side of the face appeared to be slightly swollen, and by midday a large, tense, and obviously tender swelling could be felt in the parotid region, the overlying skin being red, hot, and oedematous. Pus was exuding from the orifice of Stensen's duct, and from this a heavy growth of a coagulase-positive *Staphylococcus aureus* was cultured. The rectal temperature was 99.8° F. (37.7° C.) and constitutional disturbance was not marked. Septicaemia was not suspected and blood culture was not done. There was no evidence of infection elsewhere.

The infant was given penicillin, 50,000 units three-hourly, and the mouth was cleansed hourly. It soon became apparent that drainage was inadequate, for the swelling enlarged and became fluctuant. On October 23 a small incision was made obliquely just below the angle of the mandible, and on thrusting a sinus forceps upwards into the parotid swelling about 5 ml. of thick pus was liberated. A gauze wick was inserted, and warm sodium sulphate dressings were applied four-hourly. Drainage of pus ceased after three days. At this stage it became known that the organism was resistant to penicillin, sulphadimidine, and sulphadiazine, but was sensitive to streptomycin. Penicillin injections were therefore discontinued.

On October 28 the swelling reappeared and again became fluctuant. A sinus forceps was introduced through the original incision, and a multilocular abscess was opened, liberating a further 4 ml. of pus. A small rubber drain was inserted, and streptomycin, 100 mg. intramuscularly twice daily, was given. The drain was removed after four days, and by November 10 the discharge had ceased completely, although a small quantity of pus could still be expressed from Stensen's duct. Streptomycin was discontinued. The incision was allowed to heal, and the discharge into the mouth gradually diminished until by November 16 it had ceased. The mouth was cleansed frequently, and the infant was successfully fed by bottle on a full-cream dried milk throughout the illness.

She was seen again at the age of 13 weeks, two months after discharge from the ward, and appeared very healthy. She was taking her feeds well and weighed 12 lb. 4 oz. (5.5 kg.). There was no facial swelling, and salivary secretion from Stensen's ducts on both sides was normal. The incision had healed well, and there was no evidence of salivary fistula or facial paralysis.

COMMENT

This is the seventy-third case of acute neonatal sialadenitis to be reported, so that the condition is comparatively infrequent. The incidence quoted by Bloch and Pacella (1937), for example, is 2 out of 19,550 live births over a ten-year period, while Sanford and Shmigelsky (1945) reported 5 cases out of 10,000 live births in five years. Approximately 5,600 infants have been born in the Royal Hampshire County Hospital during the past ten years, and this is the first case of acute suppurative parotitis that has occurred. The parotid is the most commonly affected gland. Plewka (1921) collected from the literature 51 cases of sialadenitis, 41 of which were parotid infections

There are two possible modes of infection—haematogenous and ascending. A haematogenous—that is, metastatic—infection of the gland cannot occur in the absence of a pre-existing septicaemia, and evidence of its existence may not be substantiated in every case, either by a positive blood culture or by the discovery of a primary source of infection. Shulman (1950) suggests that maternal sepsis with placental transmission may account for obscure neonatal septicaemia; but this seems improbable, since most cases of maternal sepsis occur after the placenta has separated. In the present instance, with no suggestion of either maternal sepsis or neonatal septicaemia, the evidence favours an ascending infection. The mild dehydration with dry mouth about the fifth day of life, the oesophageal-tube feeding with consequent lack of reflex salivary stimulus, and the cleansing of the mouth with a gauze-covered finger may well have predisposed to ascending infection.

Immediately before the onset of this illness a minor epidemic of ophthalmia neonatorum occurred in the nursery, and phage-typing revealed that an organism identical with the one isolated from the parotid abscess was present in the conjunctivae of three affected infants, on the hands of two nursery attendants, and in the noses of four. This suggests that the abscess arose as the result of cross-infection. A suggestion that mouth-to-mouth inflation might have caused the infection was not substantiated bacteriologically, for throat swabs taken from the attendants who performed this resuscitation did not grow the staphylococcus.

Staph. aureus is the usual infecting organism, and it is well known that newborn infants are particularly susceptible to it. However, streptococci (haemolyticus and viridans), pneumococci, *Bact. coli*, *Bact. alkaligenes*, and *Oidium albicans* have been isolated by different observers.

Treatment.—Chemotherapy has not entirely obviated the necessity for incision. Shulman reported two cases successfully treated with penicillin alone, and this drug has largely superseded the sulphonamides. All but four of the reported cases treated with sulphonamides required incision. These four, reported by Neuhauser and Ferris (1945), were given two or three 125 r doses of *x* rays in addition, and recovered without incision in two to six days. They claimed that theirs was the treatment of choice, avoiding the scarring and possible sequelae of incision. On the other hand, Latchmore, La Touche, and Shucksmith (1940), in treating adult cases by this method, found that, once suppuration had occurred, incision could not be avoided. In most of the cases which they treated with *x* rays, salivary function had returned to normal within 14 days of cessation of treatment.

An incision is best made obliquely below the angle of the mandible—although Reisman and Fischer (1946) state that the risk to the facial nerve imposed by a vertical pre-auricular incision is negligible—and a sinus forceps should be thrust upwards into the abscess, exploring it until all its loculations have been broken down. The importance of this last point, and the necessity to ensure adequate drainage at the initial incision, cannot be overstressed: the risk of producing a fistula is small.

Complications of acute suppurative parotitis—salivary fistula, facial palsy, septicaemia, mediastinitis resulting from pus tracking down the carotid sheath, and rupture into the external auditory meatus—are very uncommon, but a purulent discharge from the external auditory meatus should be borne in mind as a possible mode of presentation.

I wish to express my thanks to Dr. G. Ormiston for permission to publish this case report and for his helpful comments and advice.

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Reviews

MANIPULATION

Treatment by Manipulation. By H. Jackson Burrows, M.D., F.R.C.S., F.R.A.C.S., and W. D. Coltart, M.B., F.R.C.S. Second edition, fully revised. (Pp. 80; 29 illustrations. 12s. 6d.) London: Eyre and Spottiswoode. 1951.

Every doctor should own a copy of this book, in order to fit himself to carry out at once the manipulative work called for every day in general practice. The situation that this book is designed to remedy is deplorable. Bonesetters are curing patients hourly by methods of the utmost simplicity, in spite of their lack of medical knowledge and of trained touch. We should, for the benefit of our patients, no less than the reputation of our profession, be using these measures ourselves. But we are not—to lay manipulators' pleasure and profit. This short and simple book, directed to medical men, concisely describes for the learner the techniques required at each part of the body in turn. Moreover, the novice is given a general indication of when, and when not, to manipulate, not merely how this is actually done.

It is easy to criticize this book on points of detail. Though, for example, acute torticollis and lumbago are properly ascribed to internal derangement of a cervical and a low lumbar intervertebral joint, manipulation is suggested only when other conservative measures have failed, rather than as the immediate treatment of choice. Understandably, simple descriptions like "lumbar strain," "periarthritis," "fibrositis," "footstrain" are used though they do not indicate the tissue at fault. The authors describe routine manipulation for the thoracic, lumbar, and sacro-iliac joints, whereas the budding manipulator would do better at least to localize the lesion to one of these three areas before starting; all manipulation is best performed for a defined lesion affecting one particular structure. The insistence on anaesthesia for spinal manipulation adds unnecessary difficulties to what is sometimes rather a ticklish procedure.

However, these are minor defects which do not vitiate the general usefulness of this handbook. The authors' rational attitude has brought clarity to a subject essentially simple, but for far too long clouded by exaggeration and humbug. Their followers—and I hope they will be many—by keeping manipulation within the medical sphere, will succeed not only in transferring to-day's esteem for bonesetters to doctors, but will help to obviate the dangers and social evils inherent in the performance by laymen of medical work unsupervised. It is with pleasure that this introduction to the subject is recommended to all clinicians.

JAMES CYRIAX.

RECORDING HEART SOUNDS

Herzschalldiagnostik in Klinik und Praxis. By Dr. Jörgen Schmidt-Voigt. (Pp. 116; 33 figures. M. 9.60.) Stuttgart: Georg Thieme. 1951.

This book on the diagnosis of the heart sounds in clinic and practice is an introductory account of the recording of heart sounds. First there is an introduction, clear and economical, on the basic physical and physiological considerations, recalling that the auscultatory findings have to be gauged according to their loudness, their pitch, their duration, their sequence, and their timing. The apparatus consists of a microphone uniformly sensitive over a range of 10 to 1,000 waves a second; an amplifier is introduced, and the currents pass to an oscillograph, which writes by a mirror on photographic paper. The timing is done by the cardiogram taken simultaneously. The paper should run from 4 to 10 cm. a second, according to the rate of the heart. Records of high and low frequency are recorded as needed. These records are satisfactory on the whole, but inclined to be spotty. There are many practical and useful tips on technique. It is hoped that these optical recordings will fill in the prevalent deficiencies in the teaching and skill of the art of auscultation. We are inclined to doubt it.

The author considers it probable that the valvular component, rather than the muscular, causes the first sound of the heart. After discussing the normal sounds, he has a chapter on murmurs. The general considerations are given first, all very clearly and methodically. It is surprising to read that the late systolic murmur at the apex is due to functional mitral incompetence caused by toxic degeneration of or ischaemic damage to a papillary muscle. The opening snap of mitral stenosis is said to be indistinguishable from a surface click, except with the help of a record, but the example is not convincing. The presence of a third heart sound in an adult is said to be a sign of approaching failure and an indication for strophanthin; in Britain we take a less grim view. The chapter on gallop rhythm and the extra heart sounds is altogether confused and misleading. Apart from such curious conclusions, the presentation is good and orderly. The information is well set out and clear, the headings being well planned; but the German is involved and laborious, sometimes as much as six lines without a single comma. The index is inadequate.

TERENCE EAST.

LIVER DISEASE

Liver Disease. Consulting Editor, Sheila Sherlock, M.D., F.R.C.P. Editor for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. A Ciba Foundation Symposium. (Pp. 249; 112 illustrations. £1 5s.) London: J. and A. Churchill. 1951.

This book is the record of a conference held in the summer of 1950 on certain aspects of chronic disease of the liver. The discussion ranged over a wide field, but it tended to concentrate on three problems. The first was the significance of the flocculation reactions in the plasma. These seem to depend on a fall or qualitative change in the albumin, a rise or qualitative change in the globulin, and the presence in the serum in obstructive jaundice of a factor which inhibits flocculation. Electrophoresis on paper strips, which may reveal in a simple way the physicochemical basis of these reactions, was still on the horizon, as was the correlation of chemical tests with the cellular changes revealed in the liver by biopsy.

The second focus of interest was the mechanism of ascites. This was aptly described by McMichael as one of those large central manifestations in medicine for which no single or simple explanation can be adequate. Important elements in the equation are portal hypertension, reduced colloid osmotic pressure of the plasma, increased hepatic lymph flow, and reduced sodium excretion by the kidneys. The total disturbance of the organism is less profound in post-hepatitic than in alcoholic cirrhosis, and the prognosis of ascites is therefore better.

The third major topic was the aetiology of cirrhosis, with special reference to diet, alcohol, and virus infection. A record of this kind is naturally a little scrappy and uneven, but it has been skilfully edited and well illustrated. Although it is now eighteen months since the conference, the material is highly topical and will be of special interest to those concerned with teaching or the advancement of knowledge of disease of the liver.

L. J. WITTS.

PEPTIC ULCER

Peptic Ulcer: Clinical Aspects, Diagnosis, Management. Edited by David J. Sandweiss, M.D., F.A.C.P. Postgraduate Medicine and Surgery. Published under the auspices of the American Gastroenterological Association. (Pp. 790; 164 figures. £3 15s.) Philadelphia and London: W. B. Saunders Company. 1951.

The idea of producing "an authoritative treatise embodying the best current thought on the diagnosis and treatment of peptic ulcer" was first mooted when the American Gastroenterological Association set up a committee for the study of peptic ulcer in 1946. The result is a heavy volume

containing 66 chapters on anatomy, physiology, pathology, aetiology, diagnosis, and medical and surgical treatment contributed by 74 distinguished American authorities, two Canadian, and one British. A book of this character gains from the special experience of the numerous contributors, who bring to its production detailed and personal knowledge of the different aspects of the peptic-ulcer problem, all of which cannot be possessed by any one individual. It loses by an unevenness of construction and by an almost unavoidable duplication and internal contradiction. It is, for example, difficult to see why practising physicians and surgeons (for whom the book is designed) should require detailed instruction on how to pass a tube into the stomach, and it is disconcerting to find in one chapter the forthright statement that duodenal ulcers do not cause the hypersecretion that accompanies them, while in the next the hypersecretion is attributed to interference with the normal mechanism for the control of gastric secretion, produced by the presence of the ulcer.

Such criticism, however, does not destroy the usefulness of the book; it merely serves as a warning of the necessity of reading it selectively and critically. Many of the chapters provide full and balanced reviews of their subjects and some cut through a confused literature to present clear and concise conclusions—for instance, the chapters on the relation between experimentally produced ulcers and the disease in humans and on the mechanism of ulcer pain. It is unfortunate that the American Gastroenterological Association's publication should come so soon after Ivy, Grossman, and Bachrach's monograph, also entitled *Peptic Ulcer*—particularly when the quarter of a century following the publication of Hurst and Stewart's *Gastric and Duodenal Ulcer* had seen no other major review of the subject. Comparison of the present book with Ivy's is inevitable. It is my view that the unity and consistently critical attitude of Ivy's book make his the more generally useful book of reference.

RICHARD DOLL.

ORGANIC CHEMISTRY

Organic Chemistry (A. F. Holleman). By Professor J. P. Wibaut. Translated from the 16th Dutch edition by Samuel Coffey, D.Sc.(Leyden), F.R.I.C. (Pp. 660; £2 15s.) London: Elsevier Publishing Company. 1951.

Twenty years have elapsed since the last English edition of this well-known textbook. The new author, Professor J. P. Wibaut, has produced a comprehensive account of organic chemistry—a startlingly large volume after the editions of 50 years ago intended for beginners. Full advantage of this book will not be gained unless the reader possesses preliminary knowledge, for much is greatly condensed.

The terms alkanes, alkanols, alkenes are used as general names for hydrocarbons, alcohols, etc., and the author emphasizes his inclusion of the electronic formulae for the groups. Stereo-isomerism is introduced under 2-methylbutanol-1 with mention of Pasteur's original "dissymétrie moleculaire," followed by Van't Hoff's arguments for the asymmetric carbon atom. The author briefly describes optically active silicon, nitrogen, and sulphur compounds, and the Walden Inversion. He gives many pages to describing the configuration of the pentoses and hexoses. There is less emphasis on the modern lactone formulae, which must be adopted for disaccharides and starch, with its straight and branched chains for its components. The complexity of alcoholic fermentation is indicated. The section on proteins is surprisingly good, but little is said about the chain and globular structures. The short notes on proteolytic enzymes are disappointing. The section on natural fats is below the standard of other parts; the composition of fats is pure organic chemistry. Professor Wibaut himself has been interested in the structure of benzene. Kekulé's plane structure is regarded as correct with two valency electrons between each pair of carbon atoms. In the cyclohexanes the carbon atoms are not in the same plane but can be represented by "bed" and "chair" formulae. More complex hydrocarbons than anthracene and phenanthrene are not mentioned. Space was limited for discussion of sterols and bile acids. There is a longer account of carotenoids and a succinct description of porphyrins and chlorophyll. Heterocyclic compounds are considered in the last chapter.

The book is well translated and very readable. It is rather for the organic chemist than the biologist, who will find it difficult, though a source of useful information.

R. H. A. PLIMMER.

WORLD-WIDE MALNUTRITION

Geography of Hunger. By Josué de Castro, with a foreword by Lord Boyd Orr. (Pp. 288. 18s.) London: Victor Gollancz Ltd. 1952.

This book takes us on a tour round the world, and often through the centuries, on a grand inspection of hunger and its ill effects on the individual and society. Thus we read the familiar story of famine or malnutrition resulting from floods and locusts in China, from poor agricultural methods and the use of cows' dung as fuel in India, from the excessive cultivation of the sugar cane in the West Indies, or of hunger in less spectacular forms in any other parts of the world where the inhabitants, through poverty or ignorance, are receiving diets inadequate in quantity or quality. The author does not hesitate to state his views on the sociological and political aspects of his subject, and Lord Boyd-Orr is certainly correct in his foreword in suggesting that the work might equally well have been given the title *Hunger and Politics*.

As his central theme Dr. de Castro assumes that malnutrition causes increased fertility among the prolific Oriental races. He considers, therefore, that by increasing their standard of feeding the reproductive rate would be reduced and the problem of the overcrowding of the world relieved. This conclusion is evident, he argues, from the inverse relationship which can be traced between the intake of animal protein and the fertility rate, with Formosa at one end of the scale with low protein and high reproduction, and Sweden at the other. Moreover, protein deficiency is known to cause liver injuries, and the injured liver cannot inactivate oestrogens, which for some quite unexplained reason are held to increase fertility when present in excess.

Not every reader will agree about the validity of these arguments, or about the axiom that colonial development, particularly by Britain, is usually no more than a medium for one-sided exploitation. Opinions may also differ on whether the interests of the U.N. Food and Agriculture Organization will be helped or hindered by its chairman raising such controversial points in both scientific and political fields. The book may be recommended, however, for its ability to capture and hold the reader's interest with its tale of poverty and misery throughout the world. With a saving of some of the space devoted to the airing of the author's own opinions and speculations, and the substitution of a solid core of statistics and a few good maps, the book would doubtless have permanent value.

T. MOORE.

Sometimes all that can be recorded about the effect of a drug on a group of experimental animals is that a certain number lived and the rest died. The statistical analysis of such all-or-nothing or quantal responses is often carried out by means of probits. Dr. D. J. Finney discusses it in his well-known book *Probit Analysis* (Cambridge University Press, 35s.), the second edition of which has recently appeared. He includes much else of interest on the design of experiments and the evaluation of results, and has added a new chapter on recent developments in statistical analysis. While the book will be indispensable reading to many biologists and toxicologists, medical statisticians will also find it of interest. For example, an illustration of how probit analysis was used to estimate the average age of the menarche in a group of schoolgirls is to be found in an article by Wilson and Sutherland in the *B.M.J.* of October 14, 1950, p. 862.

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THE AWARD AND THE WORKING PARTY

The report on remuneration of the G.M.S. Committee to the Special Conference of Representatives of Local Medical Committees, to be held on June 26, is printed in this week's *Supplement*. The terms of the Danckwerts Award are known, and general practitioners, to judge from the correspondence in this journal, are well satisfied with the result and appreciative of the hard work of those who have brought a long-drawn-out struggle to a successful conclusion. Mr. Justice Danckwerts applied for the year 1951 a betterment factor of 100% to the estimated necessary total remuneration of general practitioners for 1939—he thought the corresponding factor in 1948 would be 85%. It seemed logical to conclude that the factor for the year 1949–50 would be between 85% and 100%, and that the factor after 1951 would be adjusted in accordance with any further changes in the value of money. But Mr. Iain Macleod, the Minister of Health, has notified Dr. Wand, the chairman of the G.M.S. Committee, of the Government's decision on a betterment factor of 85% for 1948–9 and 1949–50, and of 100% for 1950–1 and subsequent years. This decision is bound to cause some disappointment. It is, however, not clear that the Spens Report advocated a yearly readjustment of the capitation fee, intended, in other words, to tie the size of the capitation fee to the cost of living. Nor has the medical profession, in pursuing its just claims, sought for itself a specially sheltered economic position in the community. The cost of living, after all, can go down as well as up, and the profession, of course, may at any time ask the Government to reconsider the question of remuneration.

Of greater importance than this apparent difference of interpretation of the Danckwerts Award are the methods of its allocation, drawn up by the working party of representatives of the G.M.S. Committee and of the Ministry of Health. The terms of reference were to distribute the Central Pool in such a way as to make available to the public the best possible medical service, to discourage unduly large lists, to improve the position of doctors unfavourably placed, to make it easier for new doctors to enter practice, and to encourage group practice. The Working Party recommends that the maximum number of persons on the list of a practitioner working by himself should be 3,500 instead of 4,000; that a partner should have a maximum of 4,500 instead of 5,000, provided the average for the partnership is not above 3,500 (instead of 4,000); and that the number on the list of a permanent assistant should be 2,000 instead of, as heretofore, 2,400. The suggested method of remuneration is such as to encourage acceptance of this restriction. First, there is to be a fixed capitation fee of 17s., instead of a fee which varies from locality to locality. Secondly, there is to be an additional 10s. for the 1,000 persons on a list after the first 500: in other words the capitation fee for Nos. 501–1,500 on a list will be 27s. For Nos. 1,500 to 3,500 the fee will be the basic 17s. Averaging it out, the capitation fee rises to a maximum of 23.8s. for 1,500 on a list and thereafter tapers to 19s. 10d. for a list of 3,500. The present scheme provides an average gross income of £2,905 from fees for a list of 3,500, and the new method a gross income of £3,475 for the same number. When the scheme is fully in operation no capitation fee will be paid for persons in excess of the restricted number of 3,500, with a tolerance margin of another 100.

To encourage partnerships—and therefore to help the young man to enter into his full responsibility as a principal—the Working Party has agreed to add the loading of 10s. to notional lists of partners. That is to say, if two men in partnership have a total list of 3,000 persons, the 27s. capitation fee (basic 17s. plus 10s. for Nos. 501–1,500) will be applied to 2,000 of these, even though one of them may in fact have only 900 on his list and the other 2,100. This offers a financial inducement for single-handed practitioners to enter into partnership. Another aid to the young practitioner is the proposed "Initial Practice Allowance" to be paid to those working in areas to be designated—presumably those in which there is a shortage of doctors. The allowances suggested are £600 in the first year, £450 in the second, and £200 in the third, with provisos. Finally, a sum of about £100,000 is to be set aside to introduce, if necessary, "further measures to stimulate the formation of partnerships working as a group practice."

These proposals, not entirely novel or unexpected, are bound to provoke discussion and even disagreement. But by and large they go a long way to meeting present discontents. For four years general practitioners in the Health Service have been underpaid; the Government, having accepted the Spens Recommendations, avoided acting on them. This has at last been put right—or, at least, almost right. The proposed method of distribution of the pool eases matters for the practitioner who wants to avoid a

large list. Partnership is made more attractive. The young man is getting a much-needed leg up.

Any set of proposals between two parties must be a compromise. Yet any compromise may lead to difficulties in the future which should not be overlooked now. The medical profession accepted restriction of the size of lists under the National Health Insurance Scheme, and again under the N.H.S.; and, indeed, discouragement of unduly large lists was one of the terms of reference of the Working Party. But with nearly all general practitioners working in the Health Service the question of restriction must, though accepted, be looked at critically. It may be expedient to restrict the size of lists, but as a principle it is open to attack. Restriction is bound to imply distrust, and it ignores the varying capacities for work—and for organizing work—among doctors. A man who is methodical and a good organizer can care for a greater number of persons than a man more casual and haphazard in his methods; experience and age are two other obvious factors. There is much to be said for so loading the capitation fee as to provide a man with a list of, say, 2,500–3,000 with a decent living—and to do away with restriction of numbers. It is only the few who will try to take on more work than they can manage, and when they do this their patients will seek the obvious remedy. With over 90% of general practitioners working in the N.H.S. the next numerical limit may be such as to represent the number of persons in the country divided by the number of G.P.s—possibly a list restricted to 2,500. And, if this should happen, a full-time salary will be the subject for discussion by a future working party.

The International Labour Office—an intergovernmental organization—is now once more discussing proposals for minimum standards of social security. It has received from a group of "experts" appointed by the World Health Organization a report on "medical aspects of social security." In this the "experts" condemn the method of fee for service and of the capitation fee; they favour payment by salary. If a convention for minimum standards for social security is ratified by a sufficient number of member States of the I.L.O., then payment of general practitioners by salary will come more and more to the fore in this country. The Council of the World Medical Association has within the past four weeks taken active steps to counter the view expressed by the W.H.O. "experts," and has forwarded to the I.L.O. a considered statement on the principles which should govern the provision of medical care as part of social security, including opposition to a full-time salaried service. These matters are by no means remote from current discussions on methods of distributing the Central Pool in relation to the Danckwerts Award. The Working Party has reached what in present difficult circumstances is a solution likely to commend itself to the majority of general practitioners. Nevertheless, the long-term consequences of present decisions must be carefully considered in relation to the welfare of the public as well as of the profession.

A SECRET REMEDY FOR CANCER

In September, 1950, *Picture Post* saw fit to use its columns for what purported to be an account of research into the merits of a remedy for cancer, the secret of which remained in the hands of a Mr. Rees Evans, who inherited it, apparently, from a Welsh family described by *Picture Post* as the "Healers of Cardigan." In a comment[1] on this curious episode in the long and tragic history of alleged cancer cures we repeated an observation made in this *Journal* in 1908, when the claims of Mr. Rees Evans's father were being investigated: "Cancer curing is to our mind the most execrable of all forms of quackery, for, in addition to the bitterness of disappointed hope, it inflicts an incalculable amount of unnecessary suffering."

It was a matter of surprise to many that the then Minister of Health, Mr. Aneurin Bevan, made no comment on this particular method of acquainting the public of the alleged benefits of a secret remedy for a disease now more prevalent in an ageing population than 50 years ago. He set up a specialist committee of eminent men of science and medicine so that the Rees Evans "cancer cure" should be "fully and fairly investigated." This seemed to many to be rather an unusual compliment to pay the purveyor of a herbal secret remedy, especially when there existed in the Imperial Cancer Research Fund a well-tried machinery for investigating cancer cures. But maybe Mr. Bevan was at the time swayed by public opinion as, for example, expressed at that time by Mr. Ritchie Calder, who wrote in the *New Statesman and Nation* this: "One of the most courageous and debatable journalistic ventures of our times was the *Picture Post* investigation of the Rees Evans treatment of cancer. . . . Tom Hopkinson, the editor, was showing courage also because he must have known that it would draw upon him the kind of virulent attack which the *British Medical Journal* made last week." When the question was raised again in the House of Commons 10 days ago Mr. Bevan made an observation which he might well have made a year and a half ago when he said: "Will not the

[1] See *British Medical Journal*, 1950, 2, 663, 875.
[2] Ibid., 1950, 2, 885.
[3] *Manchester Guardian*, May 30, 1952.

right hon. gentleman agree that there was something peculiarly offensive and hurtful to the emotions of large numbers of people in giving such publicity to these claims before they had been properly investigated, and that all that has been done could have been done by sending a letter to the Ministry of Health without arousing the hopes unnecessarily of so many sick people ? "

The report of the distinguished committee under Sir Robert Robinson, O.M., who was in 1950 President of the Royal Society, was completed some time ago, and the medical profession—and, no doubt, many sufferers from cancer and their relatives—have been eagerly awaiting its publication. What expenses have been incurred in the investigation and in drawing up the report have been met out of public funds, and both the public and the profession have surely the right to know what is in it. It was peculiarly disappointing to hear the new Minister of Health, Mr. Iain Macleod, say: "The report has now been received, and in the normal way I should have proposed to publish it; but as it contains information supplied to the committee in confidence by Mr. Rees Evans and by patients and their relatives I cannot do so." As to the confidential information supplied by patients and relatives, surely the confidence can be preserved by omitting from the report the names and localities of the patients treated. Medical journals all over the world record week after week openly and publicly the most intimate details of patients but as a general rule hide their identity under case numbers. This open declaration of evidence is part and parcel of scientific investigation. Is the reason, then, that Mr. Rees Evans may have divulged the nature of his remedy only on the understanding that the secret should be preserved ? When Mr. Bevan offered to have Mr. Rees Evans's cancer treatment investigated he wrote to him[2]: "I hope you will be able to accept this offer, but, in putting it forward, I must ask that you on your part will agree to abide by any decision which they may reach and, furthermore, that you will be prepared to submit to the committee, should they require it, full details of your materials and methods and will no longer insist that these can be disclosed only during the actual treatment of patients." In his reply Mr. Rees Evans said that he was perfectly willing to submit to the committee the fullest record of past cases and "whatever they may ask concerning my material and methods." He observed, too, that he thought his work could not be fully tested "unless actual treatment of patients forms part of the investigation." "The second point," he wrote, "is that I am a simple man with no scientific background."

It would be foolish to deny the possibility that a simple man with no scientific background might hit upon a great discovery, but in this age of science it is surely unwise for simple men to make claims for the treatment of such a dread disease as cancer with a remedy the nature of which is not disclosed. Mr. Macleod told the House of Commons that the committee has advised him that the claims made do not warrant further investigation and that he has accepted that advice. This was a conclusion we fully expected; but the matter should not be allowed to rest there. The report should be published. The profession and the public should know whether or not Mr. Rees Evans has disclosed the secrets of his remedy. If he has not, then the public may well wish to know whether this secret remedy should continue to be used in the treatment of human cancer. According to newspaper reports[3] Mr. Rees Evans feels he has been badly let down. "However," he is quoted as saying, "several other eminent medical people well qualified to judge are interested in my treatment and my results. I know that the opinion of this committee will not prevent others giving my treatment a real and thorough investigation."

If the expert committee's report is not published in full, if Mr. Rees Evans will not disclose the nature of his remedy, if he continues his treatment in the absence of any proper controls, then still another morbid mythology will be allowed to form round the treatment of malignant disease; and in this process there will be, to repeat Mr. Bevan's words, "something peculiarly offensive and hurtful to the emotions of large numbers of people"—not to mention their bodies. The public should insist on the publication of the report of the Ministry of Health's committee, and should insist, too, that the nature of the remedy or remedies should be disclosed. No one should be allowed to keep secret the constituents of a preparation he believes will cure, even partially, one of the most dread diseases of modern times.

MARRIAGE, DIVORCE, AND THE B.M.A.

A memorandum of evidence submitted by the Council of the B.M.A. to the Royal Commission on Marriage and Divorce was published as an appendix to the Annual Report of Council in the *Supplement* of April 19. The day after its appearance the newspapers gave it a degree of publicity which was, perhaps, a measure of the public's awareness of how close a doctor, by the nature of his work, must be to the many vexed problems of divorce. The physical and psychological difficulties of human couples bring them often enough to the doctor's consulting-

room, and in an age of decaying religious faith he not seldom is also the recipient of confessions of human frailty and perplexity. It was, therefore, with a background of wide, and indeed exceptional, experience that the committee of doctors set up by the B.M.A. approached their difficult task and drafted their proposals.

At the beginning of its arguments the committee said: "The Association, therefore, can speak with authority on the necessity for permanent and stable partnerships in marriage, and it would wish to emphasize the importance of this factor in presenting its evidence." The Council "sought to confine its attention to such of the questions under discussion by the Commission as may be regarded as medical in character or as having medical aspects." But, as health is so inextricably linked with emotional and environmental factors, "almost any aspect" (so the memorandum runs) "of the application of legislation in connexion with marriage and divorce may influence the well-being of the individuals concerned." Dr. H. Guy Dain, the Chairman of the B.M.A. Committee on Marriage and Divorce, stressed this in oral evidence before the Royal Commission last week, a report of which appears elsewhere in this issue. He also made it plain that the memorandum expressed the views of the Council of the B.M.A. and that it had not yet been considered by the general body of members. Lord Morton, the chairman of the Commission, thought it might be well to make this plain, and also "that the import of the proposals for the extension of the present grounds for divorce is not as wide as might be supposed."

Correspondence in this journal shows that many doctors are disturbed by the Council's memorandum —or rather by parts of it. The dividing line between what is "medical in character" and what is not is hard to draw in any discussion of human behaviour. Unhappiness leads to ill-health. The doctor's job is, if possible, to remove the causes of ill-health, to try to make people better, and more than ever is he to-day aware of the harm done to body and soul by the disturbed mind. Yet he should be cautious in his approach to the fundamental social structure which is marriage. In the Christian civilization of which Europe—and Britain—is still a part, the religious concept of marriage as a sacrament can no more be ignored than the legal concept of marriage as a lifelong contract. In the evidence[1] presented to the Commission on behalf of the Church of England by the Archbishop of Canterbury the dilemma of the churches is plainly stated thus: "In the nation are those who hold and apply the Christian standard of marriage. But there are very many, perhaps a majority, who do not hold it on Christian grounds, or do not hold it at all. That being so, the Royal Commission could not base its recommendations solely on the grounds of Christian doctrine." It is then, however, cogently argued that "the national standards and habits should approximate as far as possible to the Christian standard." The Church of England accepts divorce laws as inevitable but opposes "any measures which would extend the present legal provisions for divorce or would tend to weaken further the stability of the institution of marriage as a lifelong obligation."

The criticism of the Council's memorandum is on religious grounds and is perhaps best summed up by the letter in the *Supplement* of May 24 (p. 252) by those speaking on behalf of the Christian Medical Fellowship. It is because the criticism is so based, and sincerely based, that in this column we step outside the normal framework of a medical journal. Objection is levelled principally at Clauses 14, 15, and 16: the first two recommend extension of the present grounds for divorce, and the third comes under the heading "Exercise of discretion in regard to collusion." It is plain from the Archbishop of Canterbury's evidence that the Church of England is strongly opposed to Clauses 14, 15, and 16 and also to Clause 4, on "Marriage between persons of 'non-consanguineous relationship.'"

The Council's memorandum on Marriage and Divorce will no doubt be thoroughly discussed at the Annual Representative Meeting in Dublin next month. In view of the publicity already given to it the public will no doubt be eager to follow what is said. A special responsibility will therefore rest upon those doctors who come to the rostrum, and the meeting will be able to rely upon them to keep their words and emotions under control so as to cause no offence to those whose beliefs differ from theirs. And it is well to recognize frankly in advance that certain clauses in the memorandum disturb what is probably a minority in a nominally Christian country—"those who hold and apply the Christian standard of marriage."

[1] *The Church and Marriage*. 1952. The Church Information Board, Church House, Dean's Yard, Westminster, S.W.1. Price 1s. 6d.

PENICILLIN IN THE LUNGS

In certain animal species the parenteral injection of the diethylaminoethanol ester of penicillin produces a higher concentration of penicillin in the lungs than equivalent amounts of the procaine derivative or the sodium salt. Drs. J. Ungar and P. W. Muggleton, as they record on another page this week, have also found that the selective accumulation is greater if the lungs are inflamed. Although in man penicillin has been demonstrated[1] in lung tissue after treatment with the ester, the concentrations obtained have not been compared with those produced by other penicillins. The ester appears, however, to give higher concentrations in the sputum of patients

[1] Heathcote, A. G. S., and Nassau, E., *Lancet*, 1951, **1**, 1255.
[2] *Acta med. scand.*, 1952, **142**, 32.

with chronic bronchial or pulmonary suppuration. There was a considerable decrease in the daily volume of the sputum during treatment with the ester, but no comparison was made with the effects of other penicillins in the same patients under the same conditions.[1] Mulder and his colleagues[2] claim that the daily dose of ester required to eradicate *H. influenzae* from the sputum is only half that of the sodium salt. But other studies have failed to demonstrate much change in the bacterial population, although there were high concentrations of penicillin in the sputum and the volume was much reduced. Such discrepancies are not surprising. Little is known at present about the variations in the observed bacterial population of different samples of sputum from the same patient, or even of different portions of the same sample. Nor, with few exceptions, is it known which bacteria in the sputum are harmless fellow travellers and which, if any, are causing the bronchial or pulmonary inflammation.

Mulder and his colleagues have described a disease which they call "haemophilus bronchitis," defining it as a condition in which *Haemophilus influenzae* is cultured from the sputum of patients with bronchitis. But they present no evidence that will satisfy Koch's postulates to support this aetiological diagnosis. Sputum is what is expectorated, not what is produced in the bronchi. Bronchial secretions and sputum may be, but are not necessarily, identical. To draw conclusions unreservedly about the bacterial population of the bronchi from the findings in a single sample of sputum is not justified. Until the bacteriology of bronchial infections has been more scientifically investigated unsupported claims of specific aetiological varieties of bronchitis cannot be accepted. Nor can it be concluded that one antibacterial drug is better than another because it produces higher concentrations in sputum or lung tissue and appears to alter the bacterial population of sputum samples.

The value of the penicillin ester can be determined only by clinical trial, which the laboratory investigations so far reported have now justified. But it will not be easy to demonstrate any superiority over other penicillins. The effect of penicillin in many pulmonary infections is so good that a very large number of patients would be required in any trial to disclose better results with the ester, and really to demonstrate its superiority it would first be necessary to investigate more closely the action of penicillin itself. Whether the assessment of the ester is by planned clinical trial or by the collection of individual experiences in hospital and in the home, the physician will measure the effect by changes in his patients and not in their respiratory bacteria.

WELDING AND HEALTH

Welding of metals is most commonly done by means of the oxy-acetylene torch or the electric arc, and, since there is something spectacular about these methods, it is not surprising that they should be blamed for various kinds of ill-health. At the high temperatures used many elements vaporize, oxygen and nitrogen combine, and fumes are given off. Electric-arc rods are coated with fluxes, and metals to be welded are sometimes alloyed or painted with substances potentially harmful. One of the best-known risks is that of lead-poisoning: other metallic intoxications thus met with are from manganese, mercury, cadmium, and beryllium. Those in charge of the work could reduce such risks by taking expert advice. Welders have been thought to be especially prone to pneumonia, upper respiratory, gastro-intestinal, and lung disease, as well as to symptoms of general ill-health. Most of these fears are unjustified, as surveys of the health of welders have shown. The latest, by Doig and Duguid,[1] of the Factory Department of the Ministry of Labour, provides a good corrective without understating the hazards.

The evidence that welders are more than usually prone to acute respiratory disease, apart from the effects of gassing, is not convincing. Doig and McLaughlin[2] were the first to show that nodular shadows were sometimes seen on the *x*-ray films of the lungs of arc welders with long experience: this is presumed to be due to deposits of iron oxide. Their work has been amply confirmed, and it is usually agreed that this form of pneumoconiosis, however much it resembles silicosis radiologically, causes no disability because there is no fibrosis. In *x*-ray diagnosis it remains a trap for the unwary. There is some evidence that these lung shadows disappear if the welder gives up his work.[3] Pulmonary changes are less common in gas welders, who, however, run the risk of acute pulmonary oedema from inhaling oxides of nitrogen, especially if they work in enclosed spaces, as is so often the case. Arc welders are less at risk, probably because their coated rods reduce the oxidation in the arc. "Arc eye" is a specific kerato-conjunctivitis due to ultra-violet radiation; the symptoms last some days, but full recovery can be expected. A chronic symptomless conjunctival injection is often seen in welders, but there is no evidence of injury from infra-red rays. If welders work in confined spaces on galvanized metals, so that zinc fume is evolved, metal-fume fever—with shivering, pain in the limbs and chest, headache, and fever—may develop after the usual latent period; the disturbance is transient.

"ANY QUESTIONS?"

Last December the Association published in book form a number of questions and answers from the "Any Questions?" section of the *Journal*. The first impression sold out in a month, and a second almost as quickly. A third impression is now ready, and the first copies will be sent to all those whose orders have come in during the past weeks. Readers who want to make sure of obtaining a copy, after these orders have been met, are advised to fill in the form on page 19 of the advertisements. The price of the book is 7s. 6d. (postage 6d.). A second volume of "Any Questions?" is on the way, and the subjects in it have been chosen to complement those in the current book.

[1] *The Health of Welders*, 1951, H.M.S.O., London.
[2] *Lancet*, 1936, 1, 771.
[3] Doig, A. T., and McLaughlin, A. I. G., *ibid.*, 1948, 1, 789.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

FRACTURES IN THE AGED

BY

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The term "aged" is relative, depending on the physical and mental state of the patient, but in this article it will be taken to mean those over the age of 70. With the gradual increase in the expectation of life the problem of fractures in the aged has become more and more acute. Although from the surgical aspect the problem is partly solved and methods of treatment in the acute stages and during the period of rehabilitation are to a great extent standardized, the end-results of surgery still leave much to be desired. The major problems are sociological and psychological. The most urgent problem to-day is the disposal of these patients after their discharge from hospital.

Fractures in the aged occur with extreme ease, not only on account of the general osteoporosis and fragility of their bones, but also occasionally as a result of secondary malignant disease, often arising from some completely unsuspected or undiagnosed primary source. These fractures are mostly limited to certain regions of the body, undoubtedly the commonest type requiring admission to hospital being those at the upper end of the femur. Other common sites are the shaft of the femur, the wrist, the upper end of the humerus, and the spinal column. Fractures involving the knee, ankle, and elbow are relatively rare in the aged.

Fractures at the Upper End of the Femur

Fractures of the upper end of the femur are of extreme gravity in the aged. In women the fracture almost invariably occurs at the femoral neck and more commonly on the left side: in right-handed persons the right leg is apparently stronger than the left. With men fractures of the neck are rare, and the intertrochanteric fracture with complete avulsion of the lesser trochanter is most frequently encountered. Both these fractures can occur as a result of only slight violence. Sometimes there is impaction of the neck in old women and the actual fracture remains undiagnosed, but in most cases the shaft of the femur is pulled up by the gluteal muscles and deformity occurs at the site of the fracture. The classical signs are that the patient lies with the injured leg visibly shortened and with the foot completely externally rotated, owing to the fact that the centre of gravity of the femur is well outside the line passing through the centre of the hip and the knee-joints.

At this stage the patient suffers from severe shock and pain, and much relief can be obtained immediately if the rotation deformity is corrected so far as is possible. This can be done either by tying the feet together or by screwing a piece of wood about a foot (30 cm.) long to the heel of the shoe at right angles to the long axis of the foot and projecting laterally; these must be regarded as temporary measures only, while awaiting transfer to hospital. All these patients should be admitted to hospital as early as possible for radiography and the institution of treatment. Once this fracture is suspected, and while awaiting the patient's admission to hospital, the leg should be fixed by extension on to a Thomas splint. The amazing results of this form of fixation in the front line during the first world war are well known. During the second world war Charnley introduced the adjustable Thomas splint, which permits variation of both length and size of ring. Many thousands of these splints must be in store, and much unnecessary pain could be avoided if some were issued to general practitioners for these emergencies.

Hospital Regime

The admission of old people suffering from fractures at the upper end of the femur is fraught with difficulty. Their stay in hospital is necessarily prolonged, and treatment is best carried out in special wards set aside for this type of case. This is necessary because the treatment is highly specialized and both surgical and nursing staff must be enthusiasts. The wards should not be limited entirely to the aged, as a leavening of younger people and occasionally even older children gives added interest and pleasure to elderly patients.

The essence of treatment of these old people lies in the preservation of their morale, and the sight of patients recovering is most encouraging and helpful to new arrivals. A new case should therefore be placed in a bed next to a patient suffering from a similar injury who is well on the way to recovery. The healing of fractures depends on a full and adequate diet and a good vascular supply to the site of the fracture. The latter can be assured only if full mobility is encouraged as soon as possible after the fracture has been fixed. The best way to achieve this is by a daily physiotherapy class carried out in the ward (Fig. 1). The

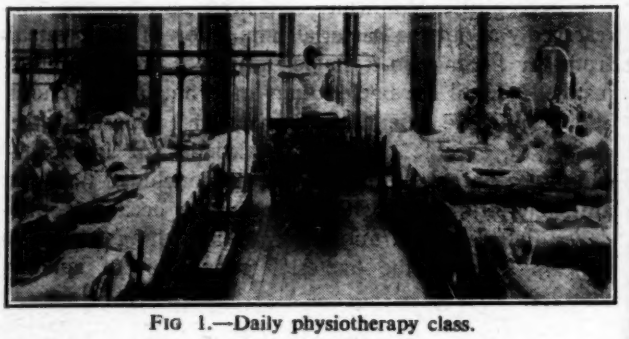


FIG 1.—Daily physiotherapy class.

physiotherapist should place herself in a raised position where all the patients can see her. Exercises are not limited to the fractured limbs but must mobilize all the limbs and the abdominal, chest, and back muscles. The patients enjoy these exercises immensely, and when the physiotherapist is on leave or for some reason unobtainable one of the younger patients is usually only too willing to take her place and supervise the exercises. In my ward all patients do these daily exercises, the only ones being excused being those aged over 90, and generally even these try to join in. Frequent baths with salt and soda in the water go a long way to loosen stiff joints once the ambulant state is reached.

The third essential is proper attention to meals. Many old people live alone in one room and feed on bread-and-margarine with an occasional cup of tea and but little else. Is it surprising, then, that their bones are so fragile and break so easily? If the fractures are ever to unite it is essential that these patients be provided with good food, attractively served, and be encouraged to eat all that is set before them. This can be done only with the help of an enthusiastic sister and nursing staff.

Surgical Treatment

Correction of the deformity of the fracture and fixation at the earliest possible date by pins or plates are the surest ways of relieving the patient of all pain and constitute the first stage to the restoration to full mobility. It must be

fully realized that, no matter how much steel-work in the form of pins, screws, nails, and plates is inserted into or on to a fractured bone, such treatment does not reduce the time of healing of a fracture by one minute. The reverse may unfortunately even be the case, for, if the steel-work results in holding the bone apart rather than well-impacted together, then union will be delayed or may never occur. When treatment by internal fixation was first used it was thought that the period of rest in bed could be considerably reduced. This unfortunately has not proved true, especially in fractures of the neck of the femur.

The blood supply to the head of the femur in old people is restricted almost entirely to that passing up the neck of the femur from the shaft; supply through the ligamentum teres is non-existent and that from the capsule negligible. Unless adequate time is allowed for the restoration of the blood supply across the fracture line avascular necrosis of the head of the femur will occur, and the pin will cut out, with resultant complications. Therefore a minimum period of 12 weeks' rest in bed is required for all fractures of either the upper end or the shaft of the femur in old people. Attempts are now being made to reduce this period of rest with the object of saving beds. Two methods are in use—the Künchner pin for fractures of the middle third of the shaft of the femur, and the replacement of the femoral head by a Judet's plastic prosthesis in sub-capital fractures of the neck of the femur. The first of these methods is firmly established, but the second is still in the experimental stage, and it is still too soon to say whether it is preferable to the usual fixation with a Smith-Petersen pin.

At the end of 12 weeks, if the appearance of the head of the femur is satisfactory, the patient gets up, wearing a bucket-top calliper, which to some extent takes the weight off the fracture line. This is worn until radiographs show full consolidation of the fracture, which does not usually occur until about six to nine months after the fracture.

Other Fractures in the Aged

Pathological Fractures.—Within the last year I have had under my care three pathological fractures of the upper end of the femur secondary to carcinoma of the breast. Internal fixation was impossible, and these patients have been treated by extension on a Thomas splint and the administration of dienoestrol, 5 mg. three times daily. The results have been remarkable: there have been bony union and almost complete disappearance of the secondary lesion, and the patients have in due course been able to walk. No untoward effects following this treatment have been observed. Dienoestrol is a synthetic oestrogen similar to stilboestrol but stronger, and consequently the dose required is smaller.

Fractures of the Spine.—The commonest fracture of the spine is a straight "concertina" compression of the bodies of one or more vertebrae, the result of marked generalized osteoporosis and minor trauma. Fixation in a plaster jacket is unnecessary and treatment by rest in bed with a firm pillow under the back is remarkably successful. Good consolidation occurs rapidly, especially if the patient is given a good diet and extension exercises for the erectores spinae in the later stages of treatment. It is unnecessary to provide any supporting apparatus subsequently; this is not well tolerated.

Fractures of the Upper End of the Humerus.—The usual fracture is the transverse one just below the surgical neck. In many cases there is impaction of the shaft into the softened and osteoporotic head. These cases require no treatment other than rest in a sling, and should never be admitted to hospital. In other cases there is overlap of the upper end of the shaft upward in front of the head. This can be reduced by closed manipulation with great ease, as muscle spasm of the pectoralis major and deltoid is negligible in old people. A roller towel is placed round the chest to immobilize the trunk. The arm is then abducted to 90 degrees under general anaesthesia and strong extension applied. It is then easy to push the shaft back under the head and reduction of the fracture can be achieved. Patients can then be treated as out-patients if the home conditions are suitable. It is by no means essential to obtain complete reduction, provided that the overlap and shortening are corrected.

Fractures of the Wrist.—The Colles fracture in an old person is a daily problem. Treatment should be carried out in the usual way by reduction under anaesthesia and fixation in plaster from below the elbow to the palm of the hand. Whereas in young people gross swelling occurs around the wrist and fixation during the first week should be by means of a posterior plaster slab only, in old people very little swelling occurs, and complete fixation in plaster at the time of reduction is possible. The blood supply to the lower end of the radius in old people is notoriously poor, and it is recommended that fixation in these cases should not be for less than 10 weeks. If one is tempted to remove the plaster earlier, displacement of the fracture only too often occurs with its associated disfigurement and poor function.

Anaesthesia

There is still considerable dispute on what is the best type of anaesthetic for open operations in old people. The main requirement is to prevent shock, and in my view the best anaesthetic is intravenous thiopentone followed by gas and oxygen, with a little "trilene" added from time to time as necessary. Local analgesics have been tried and found most unsatisfactory.

After Discharge from Hospital

The correct disposal of aged patients after discharge from hospital is most difficult. Many of them live alone; others live with relatives who are out at work all day. It is regrettable that the relatives of these unfortunate people often "write them off" and do everything possible to avoid having them back home once they have been admitted to hospital. When this happens the family doctor can give great assistance, as he will know the home conditions and any relatives who may be able to help. If it is found impossible to get the patient home, then unfortunately he must take his place among the chronic sick. In the past patients in chronic sick wards spent a large part of their time just lying in bed, but now treatment is much better, and in many cases physiotherapy departments have been opened. This has led to remarkable improvement in the patients' morale and mobility, and in many cases the relatives have been persuaded to take the patients back home again. Unfortunately the number of geriatric beds is quite inadequate and the "waiting-list" is enormous. Aged persons whose fractures have united but who still have a limited degree of mobility, and who have no suitable home to which they can return, can be well looked after in special homes for the aged, such as the Richard Cusden Homes in London. The homes are managed by matrons, and as much domestic work as possible is done by the residents; no nurses are needed, as the residents are not sick.

Back at Home

When the patient is in hospital it is comparatively easy to maintain his mobility. The beds are fitted with vertical bars and chains with handles on the end (Fig. 2). With these the patients can pull themselves up, and there is always help available when they wish to go to the bathroom or lavatory. At home one of the patient's main difficulties is getting up out of bed, out of a chair, or off the lavatory seat. For some years I have advised the provision of strong hooks, bolted into a ceiling joist and fitted with a strong rope and wooden handle, over the positions mentioned. It is remarkable how much this simple device can help.

Old people are often proud and independent and will refuse to go into a hospital for the chronic sick or a home for the aged. They prefer to return to their one room or to the home of relatives who are out all day. It is only after they have achieved their desire that they realize the terrible pangs of loneliness: patients attending hospital for follow-up constantly state their wish to be back in the ward with its bustle and happy companionship. Much is already achieved in some districts with the willing help of the Darby and Joan and similar clubs. If such a club is told that some old person is immobilized at home and alone for long periods of the day arrangements are nearly always made for more active members of the club to pay visits. It may be possible to arrange through the medical officer of health of the local health authority for a "home help" as a temporary measure. Neighbours will often help with shopping, or there may be a "home meal service" in the district. A wireless set may also be a comfort, and there are societies which help towards the cost of providing these.

FIG 2.—Bed fitted with chain and handle.

The services of occupational therapists are most useful in the treatment of fractures in old people. Patients vary considerably in their reaction to this form of treatment. Some are only too keen to carry out work, and it is often found they are more willing to do so if the work is for their own hospital. Other old people, who may never have had a proper rest in their lives before, are only too glad to lie quietly, and quite frankly cannot be bothered. Occupational therapy should not be forced on old people, but at the same time no patient in a fracture ward for the aged must be allowed to lie in bed like a log of wood.

Conclusions

In the treatment of fractures in the aged attention should be directed particularly to morale, mobility, and good meals.

Aged people suffering from fractures and requiring hospital treatment should be gathered together in special wards set aside for the treatment of such cases.

Every effort should be made to encourage the relatives and friends of old people with fractures to take them back into their own homes.

Patients who are unable to return home and who have perforce to be admitted into chronic sick hospitals should be given every opportunity for increasing their mobility by the aid of physiotherapy and occupational therapy.

The avoidance of extreme loneliness after the bustle and companionship of a ward needs urgent consideration.

Next Refresher Course Article.—"Serum Reactions and Serum Sensitivity Tests," by Drs. L. J. M. Laurent and H. J. Parish.

ROYAL COMMISSION ON MARRIAGE AND DIVORCE

ORAL EVIDENCE ON BEHALF OF B.M.A.

Representatives of the British Medical Association attended the meeting of the Royal Commission on Marriage and Divorce at Caxton Hall, Westminster, on May 28 to support orally the Association's memorandum of evidence, already presented. The memorandum was published as Appendix IV to the Annual Report of Council in the *Supplement* of April 19 (p. 188). The deputation was led by Dr. H. Guy Dain, and its members were Dr. Annis Gillie, Dr. J. A. Hobson, Dr. Doris Odlum, and Dr. A. Walk, with Dr. E. E. Claxton (secretary).

The Chairman of the Royal Commission (Lord Morton*) said he wanted to ask a question about two proposals in the memorandum: (1) that it should be possible for a petition for divorce to be presented by either party or by agreement by both parties jointly, and (2) that in certain circumstances it should be possible after a time for the offending party himself or herself to sue for divorce. These proposals had caused considerable stir both inside and outside the British Medical Association, and he wanted to find out how far they represented the views of the Association's 65,000 members.

Misapprehensions about the Report

Dr. Dain said he was anxious to make a statement in view of the publicity which the document had received and the misapprehensions which had been aroused. The Council of the Association set up a special committee to prepare evidence, and that committee had endeavoured to answer certain of the problems which confronted the Commission, restricting itself closely to the terms of reference. It had been so successful in this last intention that it—and through it the Association—was now accused of wishing to make divorce more easy. It had not expressed any views on the sanctity of marriage as a permanent life contract, and not much was said about it in the document. But, unfortunately, a summary was presented in front of the main document, and people read the summary without reading the argument. The committee represented not only the British Medical Association but to an extent also the Medical Women's Federation and the Royal Medico-Psychological Association. But it had made no attempt to express the religious or ethical views of 65,000 doctors. It had addressed itself entirely to medical problems arising out of the divorce laws and to changes which they thought would make those laws more effective. It had accepted divorce as part of the structure of present-day society and had attempted to give the Commission advice on which improvements might be brought about. It laid stress on preventing divorce by various means which were suggested and spoke of methods whereby anomalies could be straightened out. It was due to the witnesses that this should be stated at the very beginning in view of the public misapprehension of the Association's attitude.

Lord Morton said the Secretary of the Association had stated that the Council had no objection to the publication of its proposals after the oral evidence had been given, but in fact the proposals were published and reached the Press before the witnesses appeared before them, and before there was any opportunity of elaboration or explanation by oral evidence. The proposals were seized upon by the Press for their news value, and it was widely thought that the Association had gone beyond the medical field and expressed a wider point of view. This had caused considerable perturbation; the Commission had received many letters from doctors who had disclaimed these views, and he had seen correspondence in the *British Medical Journal* to the same effect.

*Lord Morton of Henryton is a Lord of Appeal in Ordinary. He was created baron in 1947.

The Chairman went on to quote from the memorandum:

"It is not the practice of the Council to make pronouncements on matters of public policy concerning which medical practitioners may hold views as individual citizens but cannot claim to speak with special authority in their professional capacity. . . . It should be stated, however, that health, including mental health, depends so much upon emotional and environmental factors that almost any aspect of the application of legislation in connexion with marriage and divorce may influence the well-being of the individuals concerned."

Were the proposals which the Association was putting forward for an extension of the present grounds of divorce a general expression of the opinion that such extension would make for the mental health of the people who wanted divorce? It was now said that these proposals had a limited scope, but as originally set out they appeared to have a very wide scope indeed.

The following dialogue then ensued:

Lord Morton: It is clear from letters in your *Journal* that there was a lack of consultation with the body as a whole before this memorandum was issued. As you have 65,000 members, are they divided into branches?

Dr. Dain: They are.

Lord Morton: What steps were taken to bring this memorandum to the attention of the general body of practitioners and obtain their views on it?

Dr. Dain: The notice of the request from you and the establishment of the Special Committee were published in our *Journal*. The report of the committee was considered by the Council, who represent the whole of the members from all over the country, and it was agreed that it be presented as expressing the views of the Council. We have taken no steps to bring it to the special notice of the individual members, but it will come forward for consideration at the Annual Representative Meeting in July. The conditions under which the evidence was prepared were urgent; you required an answer by a date which you were kind enough to extend, but we have had no opportunity to go to our constituents.

Lord Morton: I am not criticizing the procedure you followed; I merely wanted to get it plainly before us how far individual members were involved in this. These are the views of your Council?

Dr. Dain: Yes.

Lord Morton: And they have not yet been considered by the general body of the members?

Dr. Dain: No.

Lord Morton: I think it might be a good idea if you could take some steps to make it plain that these are the views of the Council, and also that the import of the proposals for the extension of the present grounds of divorce is not as wide as might be supposed.

Dr. Dain: I think we can adopt that suggestion.

Insanity as a Ground for Relief

Sir Russell Brain then took the witnesses through that part of the evidence which related to mental disorder as a ground for relief. One of his questions was why insanity had been singled out to the exclusion of other illnesses which might be almost equally destructive of married life.

Dr. Walk, who answered most of the questions in this part of the examination, said that this same question was raised in the Royal Commission of 1912. It was certainly well argued that insanity was a disease in every sense of the word, and not to be treated differently from other diseases. But the question of inclusion and exclusion was not one which could be answered "Yes" or "No." Insanity could not be assimilated with other diseases in every respect. The special committee had rather accepted the view that insanity as an exceptional ground of relief had come to stay, and that the provision had worked reasonably well for some years. They thought there was no reason to reconsider the whole question afresh, but they were concerned to remove anomalies.

Sir Russell Brain said that there was an operation called leucotomy which had made possible social recovery to some extent. Would the witnesses like to say whether in most of these cases there was some residual abnormality? Dr. Walk said they had been very much exercised over the question of people who had made a partial response to treatment, leucotomy or other, and that was one of their reasons for wording their recommendation as they had done. There had been some suggestion that personality changes should be a ground of relief, but they felt that the recommendation should remain as it stood.

Asked by Lady Bragg how many women doctors subscribed to the point of view put forward in the memorandum, Dr. Doris Odlum said that the Medical Women's Federation formed an *ad hoc* committee on the subject, and the findings had been endorsed by the Council of the Federation, but they had not been before the individual members.

Mr. Beloe, taking up a remark in the memorandum about the role of the medical adviser, asked whether the best person of all as a medical adviser would not be a general practitioner. Dr. Dain replied that that was so, but that did not mean that the whole matter necessarily rested with the general practitioner. Mr. Beloe said that the general practitioner knew the family and other circumstances better than any medical authority who could be brought in from outside. He also asked whether, in the opinion of the Association, the bad home was better or worse than the broken home. Dr. Doris Odlum replied that a great deal of thought had been given to that question, and the experience of Guidance Clinics had been taken. There was no statistical evidence, and only individual opinions could be given. For her own part she thought that the unhappy home, the scene of frequent quarrels, was worse for the children than the broken home, provided a satisfactory parent relationship was established in the latter. It was very difficult to say categorically whether the quarrelsome home was better or worse for the child than a state of affairs in which his loyalty was divided between the two parents. Each case must be considered on its merits.

The recommendation of the Association that a petition may be presented on the ground that the respondent had been suffering from mental disorder continuously for five years, that his recovery was extremely unlikely, and that at the time of presentation he had been resident as a patient in a mental hospital for a year was also commented on by Mr. Beloe, who asked how a court was to be satisfied that there had been a condition of mental disorder for five years, the patient not having been all the time in hospital. Dr. Walk replied that there was evidence in every case; as full a history as possible was taken, and some form of treatment recommended. Mr. Beloe said that apparently the five-year period might be determined on the diagnosis of a single medical practitioner. Dr. Walk replied that the evidence would have to be weighed in each instance, and if there was a conflict of evidence he imagined the most conservative opinion would prevail.

Dr. Mary Baird asked the opinion of the witnesses as to the extent of collusion in divorce. Dr. Annis Gillie said that in her own experience such cases were very few. Dr. Doris Odlum said also that not many cases had come under her observation, but she had heard a number of others speak of such cases.

Consanguinity

Sheriff Walker took up the recommendation of the Association that prohibition of marriage between non-consanguineous relations should be removed. Was it realized that this would enable a man to marry his son's widow? Dr. Dain pointed out that in the memorandum it was distinctly stated that medical grounds only were considered. From the medical point of view there was no reason for continuing certain restrictions on persons as to whom they might marry, provided that the spouses were not blood relations in any sense. They were not entering into controversy as to whether there should be social or moral prohibitions. They put it no higher than their concern over blood relationship.

Sheriff Walker also asked whether there was any recognized definition of mental disorder or insanity. Dr. Walk

replied that there was a definition for legal purposes, but of course there could be no precise boundaries. Sheriff Walker then asked what degree of mental disorder there must be to justify relief. The Association had spoken of incurable mental disorder, but it was really only a question of degree. Dr. Walk: "We had in mind mental disorder of a type which made marriage impossible."

Another member of the Commission questioned the recommendation that the ground of a petition may be that the respondent "is suffering from mental disorder which has been present continuously for a period of five years, and that his or her mental state is now such that recovery is extremely unlikely. . . ." Why bring in the five years? Why not simply say: "suffering from mental disease and his or her mental state is now such that recovery is extremely unlikely"? The important thing was that the mental state was "*now* such." Dr. Walk said that he personally would have no objection, but he thought it would not be acceptable to public opinion.

Length of Gestation

Lord Keith asked a question which did not arise out of the memorandum. Difficulties had arisen in the courts on the question of length of gestation, and of course the period of gestation was often an important piece of evidence when there was suspicion of adultery. He had heard that the medical profession might be able to arrive at a conclusion as to what was the minimum and what was the maximum period, and such might be accepted as a rule for courts. Was this possible in the present state of knowledge?

Dr. Dain replied that a case was recently reported in which the alleged length of gestation exceeded all previous ideas on the subject. He had no personal knowledge of the facts of that case, but if it were established it would mean that the period from conception to birth might possibly be not far short of a year in certain cases. He did not think the medical profession was in a position to fix maximum or minimum dates.

Lord Keith also said that there was a reference at the end of the memorandum to the application of the proposals to Scotland. The Commission was going to sit in Scotland. Dr. Dain said that it could be arranged for evidence to be given on the proposals as they affected Scots law.

The final question was put by Sir F. Burrows, who, taking up the recommendation that the woman partner in a nullity suit should have the opportunity of examination by a woman doctor, asked whether there was any difficulty in the way of such an arrangement. Dr. Dain said that there was unwillingness on the part of some authorities to provide a woman doctor; the compilers of this memorandum wanted to make it compulsory that a woman doctor should be employed in such cases.

HOSPITAL ADMINISTRATORS' CONFERENCE

CRITICISMS FROM THE PATIENT'S POINT OF VIEW

The Institute of Hospital Administrators celebrated its jubilee by holding a conference in London from May 8 to 10. The most lively of the sessions was that devoted to the patient—for whom, after all, the hospital exists—when the discussion was opened by Professor RICHARD M. TITMUSS, professor of social administration in the University of London.

In range and complexity, said Professor Titmuss, the hospital had few rivals among social institutions. A large fund of intelligence and cultivated common sense, upon which hospital administration in this country had always been able to draw, was no longer sufficient. The hospital administrator must also have a wide knowledge of the health services as a whole, a grasp of the functions of the many different departments of a modern hospital, and at least a nodding acquaintance with medical terminology. Most of the lay members who were appointed to regional boards or management committees were pretty useless during their first year. Their lack of workmanlike knowledge of the complexities of the modern hospital system encouraged behaviour round the committee table which was either sentimental or grandiose or both.

Three Main Dangers

Professor Titmuss saw three main dangers in hospitals as at present administered. The first was that increasing complexity in structure and function would lead to increased cost without a proportional rise in the value of the service. The more complex the situation the harder would it be to put a finger on the source of inefficiency. The second danger was that the end and aim of hospital administration might be obscured by excessive preoccupation with the means. The National Health Service had added immensely to the volume of administrative work in connexion with scales of reward, conditions of service, and so on, and innumerable small anomalies had continually to be ironed out. All this meant that the hospital tended increasingly to be run in the interests of the staff rather than of the patients.

The third danger arose from scientific and technological advances, which had entailed great division of labour and professional fragmentation, with the creation of specialisms, all of which meant that more people with different functions and skills were brought into contact with the patient. This happened to a patient who was almost as sick in mind as he was in body and least able to meet the strain of entering into new personal contacts with strange individuals endowed with all the authority and mystery that surrounded the hospital.

The Barrier of Silence

Professor Titmuss criticized what he called the discourtesy of silence in hospital, which was due to want of imagination. Here was a patient in need above all things of some simple explanation and reassurance, and he was examined by a surgeon who never uttered a word. The complaint of the patient afterwards was, "Nobody told me—nobody asked me." People were discharged from hospital bewildered and disillusioned because medical magic had not apparently or yet yielded its result, and they were left ignorant of what the investigation had shown.

Why was it not understood by hospital staffs that courtesy had a therapeutic value? Was the barrier of silence a device by medical authority to buttress itself? He complained also of the practice of talk between doctors or between doctors and nurses while the patient was going under the anaesthetic, for the sense of hearing was the last sense to go.

The speaker added he did not wish to leave the impression that hospital staffs were deliberately harsh. These things were done unthinkingly by people devoted to their calling. They were the result of departmental preoccupation.

Not all Professor Titmuss's views found acceptance in the subsequent discussion. One administrator said that patients entered the hospital with faith in what the hospital was going to do for them, and if they received elaborate explanations from day to day that faith would disappear. This speaker, faced with an operation, would prefer a surgeon with a cold, abrupt approach rather than one with the fussy bedside manner.

The Hospital Management Committee

Mr. F. S. STANICLIFFE, chairman of the Association of Hospital Management Committees, said there was a feeling in some quarters that these committees should be more democratically elected, but there were serious objections to this. The areas of hospital management committees did not coincide with local health authority areas, and it would be difficult to define the electorate. Moreover, if hospital management committees were democratically elected it would follow that the same principle should apply to regional hospital boards, and this would be a sheer impos-

sibility. He was "scared stiff" lest the hospital system got wrapped up in any shape or form with party politics, whether to the Right or Left. The member of a management committee was unlike the member of a local authority; the latter was a watchdog for the public, the former a manager of an institution.

It was also claimed, said Mr. Stanicliffe, that no paid employee of the hospital service should sit on the committee. In principle this was sound, but in the voluntary hospitals the medical profession had formerly taken a very large part in the actual running of the hospital, as distinct from the clinical work, and, of course, in the local authority hospitals there had been medical superintendents. Therefore there were good historical reasons, at present at any rate, why medical men should be eligible to serve on hospital management committees; he did not think the same applied to nurses or to other grades of staff. Some medical men forgot that once a person was nominated to the committee he was in no sense supposed to represent the people who had nominated him. A number of the medical profession took the view that the medical men who sat on hospital management committees represented their local colleagues. This was emphatically not so; they sat on the committee, like anyone else, to help in the running of the hospital.

The Regional Hospital Board

A description of the work of a regional hospital board, that of Birmingham, was given by its chairman, Mr. V. W. GROSVENOR, and he also described the relation between the board and the governing authority of the teaching hospitals. There was a standing joint committee with an equal number of members from both sides. At first the local executive council was also represented; but it was found that the problems which arose were almost entirely confined to the hospital service, and the representation of the executive council was now brought into action only when matters directly relating to general practice were concerned. The decisions of the joint committee were only advisory, but in no instance had either board refused to accept them.

Unpleasant Decision

Miss P. HORNSBY-SMITH, M.P., Parliamentary Secretary, brought the greetings of the Ministry. Referring to the growth of the hospital service, she said that she knew some sighed for the good old days, but the return to them was impossible, if for no other reason than the financial one. The total income from endowments transferred from the non-teaching hospitals for 1948 would pay for the present hospital service only for 22 hours of the year. Only the taxpayer had broad enough shoulders to bear the cost of the Health Service, and even he wriggled a little from time to time.

Central control, added Miss Hornsby-Smith, in no way diminished the responsibility of the hospital secretary. They all disliked economies, but the Government was right in making the unpleasant decision that the expenditure should be kept within bounds. Economies did not mean that the hospital service was standing still and that there was no development. Apart from any increase in estimates, much could be done by reorganization of existing resources to develop and improve the service, and this, so far from leading to increased expenditure, would in the long run reduce it.

The director of the tuberculosis division of the New Zealand Health Department, Dr. J. M. Wogan, recently told the Auckland Rotary Club that the Maori is now showing more resistance to tuberculosis. This is important, because of the 2,000 new cases of tuberculosis discovered in New Zealand every year one-quarter are Maoris. Dr. Wogan said rapid progress was being made, and within five to ten years tuberculosis should not be the problem to the community it is at present. The disease now costs New Zealand £5,000,000 a year.

Preparations and Appliances

A HYDROSTATIC BAG FOR DILATATION OF THE CARDIA IN ACHALASIA

Mr. HAROLD BURGE, F.R.C.S., honorary surgeon, West London Hospital, writes: In this country most surgeons interested in achalasia of the cardia treat the condition by dilatation and reserve Heller's operation for cases in which the oesophagus is tortuous and for cases in which dilatation has failed. Dilatation is usually achieved by means of a hydrostatic bag passed through a long wide-bore oesophagoscope. This method has the disadvantages that general anaesthesia is required for it and that such a wide-bore instrument has to be passed. The method here described requires neither anaesthesia nor oesophagoscopy, and full dilatation may be carried out in those cases in which the oesophagus is not tortuous.

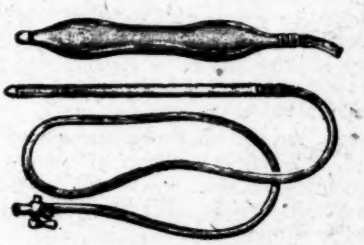


FIG. 1.—The instrument.

The instrument consists of a hydrostatic bag, 6 in. (15 cm.) long, attached by a screw joint to a flexible rubber tube of small diameter (Fig. 1). When the bag is in position it is inflated by a syringe with thin barium solution. It should not be boiled, nor should an oily solution such as lipiodol be used to fill it. A spare bag is supplied by the makers, but this will seldom be required if these precautions are taken. Since no anaesthesia is required dilatation may be done on the out-patient, but I prefer to keep my patients in hospital for one night. One hour after "omnopon" sedation the tube is passed in the ward. It passes more easily than a Ryle's tube because of the rigid yet flexible nature of the bag. The patient is then placed on the *x*-ray table and screened. When its centre is seen to lie at the cardia the bag is filled with thin barium solution. Its position is easily seen on the screen because of the metal core on which it is made. When the cardia is fully dilated a permanent record may be made by taking an *x*-ray photograph (Fig. 2). Full dilatation may be maintained for a few minutes before the bag is deflated and the tube withdrawn.

FIG. 2.—The bag in position.

Some may think it wise to confirm the diagnosis of cardiospasm by oesophagoscopy before dilatation with this instrument is carried out. I have not always done so, for I do not believe that this bag will pass through the cardia in cases in which oesophageal dilatation is due to neoplasm.

As full dilatation is reached the patient feels pain in the lower chest, and I have come to regard this as a safeguard against oesophageal rupture.

This method has proved so simple for the patient that a greater effort may be made to control the symptoms by repeated dilatation, if necessary, than is usual with the methods at present used. The instrument has been made for me by the Genito-Urinary Manufacturing Co., Ltd.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Social Trends and Home Confinements

SIR,—I agree with much of what Dr. W. N. Leak says (May 24, p. 1135) and sympathize with his point of view. Like him, I had the pleasant experience of my wife having her babies at home, incidentally made more comfortable and enjoyable for all concerned by the presence of a cook, housemaid, and a resident midwife. There are one or two matters of fact which should be considered, however. He says: "By and large, domiciliary midwifery with a competent midwife and doctor is safer and more economical—financially and in man and woman power—than institutional."

First with regard to safety, the maternal mortality is now one-sixth and the stillbirth rate nearly one-half of what it was 15 years ago, and this great increase in safety has coincided with an increase in hospital confinement. In Scotland the number of beds has been more than doubled, and in the City of Aberdeen there are more than three times as many as in 1937. During the years 1946–50 12,000 women were booked for confinement in hospital, and of these two died. If the maternal mortality had been similar to Scotland as a whole there would have been about 20 deaths.

In the city of Aberdeen in the years 1946–7, the last two years when any substantial proportion of primiparae were delivered at home, the stillbirth rate was 30% higher in domiciliary than in hospital primiparae. The stillbirth rate was higher in domiciliary cases at each parity, despite the fact that multiparae with a bad obstetric history were referred to hospital. By selection of "bad risk" cases for hospital delivery it is possible to reduce the foreseeable stillbirths greatly, but complications such as prolapse of the cord and malpresentations still occur quite unexpectedly and can be dealt with more effectively if the patient is in hospital.

With regard to economy in woman power, it is difficult to see how a midwife's time is saved if she has to walk around from one patient to another instead of being in one place with all facilities to hand and having the patient come to her. In domiciliary practice only the privileged few have the midwife available after the confinement for more than a small part of each day. With regard to expense, we require careful examination of this aspect of the problem, since I feel sure that domiciliary practice is not so inexpensive as many suppose unless standards are sacrificed. I have discussed this in more detail elsewhere (Baird, 1951, *Hlth Bull. (Edinb.)*, **9**, 66).

I have stressed in previous publications that the risks of childbirth are dependent more on the health, physique, and age of the mother than upon the attendant, since under ideal conditions most confinements should be normal. The fact is that even in countries, like our own, with a high standard of living many women have a relatively low standard of health, physique, and diet, and many postpone the first child till long past the optimum age, so that trouble does arise frequently. As a result a very high standard of antenatal and intranatal care is necessary to achieve low mortality figures. In England and Wales the stillbirth rate is about 23 per 1,000 births. There is no physiological reason why it should be more than 10, but without great improvements in health and changes in reproductive habits this would be impossible. Meantime a very high standard of obstetrics is required to keep the rate as low as it is. There are so many competing claims on the nation's resources that the attainment of the lowest possible stillbirth rate may not have a very high priority, but there is evidence that an increase in domiciliary midwifery would be a retrograde step from that point of view, nor would it lead to any economy in man or woman power.

Dr. Leak says that domiciliary practice means "safer midwifery, happier parents, and happier homes." Happiness is difficult to measure, but mortality figures suggest strongly that it is safer to be confined in hospital.—I am, etc.,

Dept. of Midwifery, University of Aberdeen. DUGALD BAIRD.

Local Aureomycin for Aphthous Stomatitis

SIR,—Like Dr. Edward Prettejohn (May 17, p. 1082), I also read of the report by Distelheim and Sulzberger (*J. invest. Derm.*, 1949, **13**, 115) on the use of local "aureomycin" in aphthous ulceration of the mouth, and I have been using it since June, 1950.

I would agree with Dr. Prettejohn that aureomycin applied locally to ulcers in the mouth may produce considerable benefit. I have been using 250 mg. suspended in 10 ml. water, used as a paint four or five times a day. Unfortunately in my experience the aureomycin works dramatically at first, but in successive attacks of ulceration its effect gets less and less, and after the fourth or fifth recurrence loses its power completely.

I chose as test cases patients who had suffered from recurrent painful ulcers for at least five years, and though local aureomycin gave them considerable relief during the first six months in which it was tried the ulcers now are as bad as ever and aureomycin no longer produces benefit.

Three cases where local aureomycin had ceased to be of benefit were admitted to hospital and given oral aureomycin 0.5 g. six-hourly for periods of 7 to 14 days without benefit. One case developed fresh ulcers whilst receiving this treatment. On the other hand, local aureomycin may be of great benefit in isolated chronic ulceration of the mouth, and the following is an example.

An edentulous woman of 59 was referred from the dental department in June, 1950, with a chronic granulomatous ulcer on the right lower alveolar margin. She had not worn dentures for a year because of the ulcer. The ulcer measured 1.5 cm. across and had a raised indurated edge with a painful sloughing centre. There was no enlargement of the regional lymphatic glands. A biopsy showed no evidence of neoplasm, but only a chronic inflammatory reaction. Blood W.R. was negative. The ulcer was treated until November 8 with paintings of gentian violet and mouth washes of glycothymol, with no improvement. Two small aphthous ulcers developed on the left cheek and the right upper alveolar margin on that day, and painting with aureomycin, 250 mg. in 5 ml. water, was started. By November 22 the aphthous ulcers and the chronic granulomatous ulcer had healed.

Aureomycin was stopped and the ulcer remained healed until December 20, when after trying to wear her dentures a small ulcer developed in the centre of the scar. Aureomycin was again started and the ulcer healed in a week and has remained healed.

It would appear, therefore, that locally applied aureomycin may be of value in clearing up a particularly severe attack of aphthous ulceration and in some chronic inflammatory ulcers, but unfortunately it is not the answer to recurrent aphthous ulceration.—I am, etc.,

Sheffield. I. B. SNEDDON.

Hospitality for Overseas Visitors

SIR,—May I once again appeal to members through your columns for offers of hospitality for our overseas medical visitors from the Dominions and Colonies? As a result of a similar appeal last year (*Journal*, May 12, 1951) we received offers which were sufficient to cover our needs, and the visits which took place were much appreciated by our overseas friends. This year we expect a goodly number of overseas medical visitors, and there will be many among them who will much appreciate the opportunity of meeting us in our homes and so getting to know us better.

I shall be very glad if doctors willing to offer hospitality to an overseas visitor for one or two days, or even longer, would write to me stating what they are able to offer.—I am, etc.,

Empire Medical Advisory Bureau, B.M.A. House, Tavistock Square, London, W.C.1. H. A. SANDIFORD.

Family Planning

SIR,—As medical officer of a family planning clinic (see May 24, p. 1132) for some 12 years, I would suggest that all patients attending can be divided into two groups : the medical and the non-medical. The medical include the patients with tuberculosis, asthma, heart trouble, kidney trouble, pelvic disproportion, debility due to numerous rapid pregnancies, etc. Nearly all of them have been warned against the danger of pregnancy—yet there the advice has often ended and they and their husbands have spent months and years of doubt and misery.

The non-medical cases can be subdivided into the over-fertile, the under-fertile, and the unhappy. The over-fertile : usually a couple who married young and at the age of 25 have already the four or five children to which they feel they can do justice. This group also includes the mothers of "problem families." They are frequently loving mothers of great fertility and low mentality. If helped and encouraged by kindly, patient handling they have a new lease of life when delivered from the fear of the 11th or 12th pregnancy. I feel that a great service has been done to the community when one of these women has become a regular attender at our clinic.

The subfertile : after years of marriage have had no pregnancy. Here again time and patient accurate history-taking are essential.

The unhappy : this large group includes the vast numbers of young people who "have the use of a bedroom in mother's house." They have two children in a cot and the baby sleeps in a basket on the dressing-table ; there is no place to put a social worker however helpful. If the friction between in-laws or with a landlady becomes unbearable they buy a house, and the financial strain is so great that the mother tries to get back to work. Some of these young wives have spent the early years of the marriage terrified of pregnancy, and as a result have developed a hatred of the physical side of marriage and are well on the way to a marriage breakdown.

In trying to control fertility we have no wish to attempt to alter human nature. Those couples who love children and have the right temperament for bringing them up will have them whatever the conditions. They never dream of coming to a clinic until they have had as many children as their health and finances can possibly stand.

Having had four children myself in under six years I am in a strong position to advise those women who from fear of childbirth or hard work "space" their families indefinitely to one or two. Even couples who appear to be in this class frequently have inapparent but extremely adequate reasons for limiting their families. These reasons come out when they like and trust the doctor who interviews them at the clinic.

Dr. Hastings Sayers (May 24, p. 1135) wonders why women doctors have not entered the fray on female sexual disorders. Perhaps because we believe in prevention rather than trying to find cause and cure.

I would suggest that if all engaged couples attended a course (such as that recommended by the Marriage Guidance Council), including a talk on ovulation, sperm production, and mentioning proper sources of contraceptive advice, numbers of these disorders would never arise.—I am, etc.,

Liverpool. ISABEL M. GARDNER.

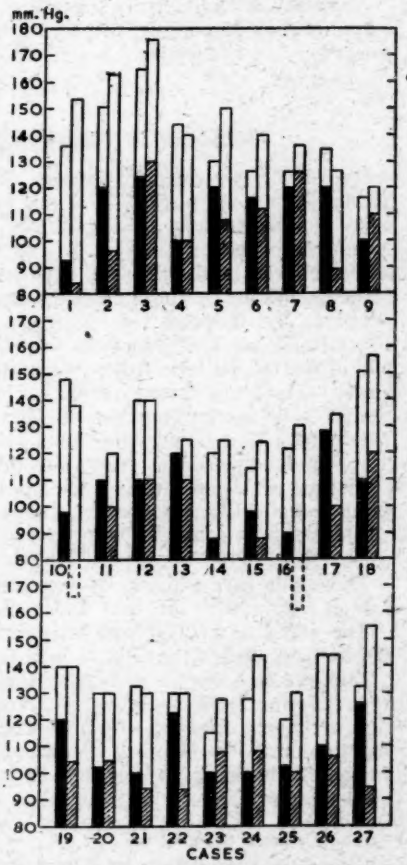
SIR,—Dr. Agnes R. S. Sadler (May 24, p. 1132) agrees "that widespread contraceptive practices flourish"—the question is, What practices ? If doctors will not make scientific advice available to those who want it, the result will be a widespread use of other means, many of which are undesirable and some definitely harmful. It is estimated that there are many tens of thousands of criminal abortions every year in this country.—I am, etc.,

London S.W.1. IRENE M. JAMES.
General Secretary,
Family Planning Association.

Management of Hypertension

SIR,—I have read with much interest the article by Professor J. McMichael (May 3, p. 933). I feel, however, that I must join issue with him over his summary condemnation of sympathectomy as a method of treatment.

While in this centre our experience of this operation is not numerically large, it now extends over five and a half years, during which time my colleague Mr. J. Hardman has performed the Poppen operation on some 60 cases, representing only 15% of the 400 patients seen at a hypertensive clinic within this period. I have had occasion recently to take stock of 32 of these patients (21 men, 11 women) whose post-operative follow-up now ranges between two-and-a-half and five years; 27 of these patients survive, three having died from complications of hypertension and two from other causes. In the accompanying chart the diastolic blood pressures at the end of this period, both lying and standing, have been compared in each case with the pre-operative levels. My object in showing these figures is to draw attention particularly to the fall in the standing diastolic pressure which persists at the end of this period. The average reduction in standing pressure is in fact 36 mm. Hg, and in only a single case is it less than 10 mm. Hg.



Twenty-seven sympathectomy cases. Lying and standing diastolic pressure at last examination (average three years after operation) related to pre-operative levels. Left half-columns = lying diastolic pressure. Right half-columns = standing diastolic pressure. Pre-operative, unshaded. Post-operative, shaded.

Professor McMichael has formed a poor opinion of sympathectomy since recumbent blood pressures are often found to return to hypertensive levels within a year or two of operation. In view of the importance he attaches in his paper to the postural hypotension which follows parenteral administration of hexamethonium bromide, it is surprising that he appears to have given no thought to this similar effect of sympathectomy. In my opinion the vascular relief afforded by sympathectomy is in fact largely due to the postural hypotension during the hours which the patient spends upright, and our experience so far suggests that after a sufficiently extensive denervation this postural hypotensive effect is likely to be well maintained.

Were Professor McMichael able to interview the small group of patients to whom I have referred he would, I believe, be left in no doubt that they at least share my opinion that their operation has been worth while. I think also he would find them a great deal happier than his own group of patients who have to inject themselves with hexamethonium bromide. Not only have their headaches almost universally been relieved but all are leading normal, active, and unsupervised lives. To quote only one example, the third patient in the table, whose diastolic blood pressure previously ranged between 160 and 170 mm. Hg, has now worked without interruption for three years at a coke oven.

In justice to the surgeons alone I feel it must be stated that some of us with adequate experience retain full con-

fidence in this operation, and are likely to continue to recommend its performance in selected cases of hypertension.—I am, etc.,

Sheffield. A. W. D. LEISHMAN.

SIR,—I invite Dr. H. Warren Crowe (May 31, p. 1191) to read a paper by David Ayman (*J. Amer. med. Ass.*, 1930, 95, 246), in which he described the exhibition of dilute hydrochloric acid to patients with essential hypertension with successful symptomatic relief in 82% of cases (40). Ayman, naturally unacquainted with the work of Selye, concluded properly that this result was in line with "many of the last decade's 200 or more successes in the therapy for essential hypertension," including the use of extracts of mistletoe and of watermelon, all of which have passed into limbo—or so one thought. The common factor in all these "successes" is undoubtedly suggestion, for "drugs may not cure, but they do console," especially if their taste and their prescriber are impressive.—I am, etc.,

London, W.1. JOHN HAMBLING.

Blindness in Northern Nigeria

SIR,—I was interested to read Dr. G. E. Dodds's memorandum (March 15, p. 584). For the past six months I have been making surveys of eye disease in certain areas of Northern Nigeria. Samples of the general population, schoolchildren, and prisoners have been examined. Also patients suffering from eye disease have been collected at dispensaries and hospitals for me to see. These surveys only cover small areas of Northern Nigeria, and were carried out in Bornu, Bauchi, Adamawa, Zaria, and Plateau Provinces. The blind persons seen have been analysed, using a similar classification to that of Dr. Dodds. He records "leucoma, phthisis, and staphyloma" as one group. I have, however, subdivided this group into three subgroups:

(*a*) Those who gave a history of "bakwondoro," a local word which covers chickenpox, measles, and septic skin conditions.
(*b*) Those who gave a history of smallpox.
(*c*) Those who gave a history of local eye disease only.

Those who gave a history of penetrating injury causing the loss of vision were included under the heading "trauma."

The standard of blindness used was inability to count fingers held against the light at a distance of two metres.

Multiple pathology is common. For instance, one patient was suffering from onchocercal choroido-retinal degeneration, trachoma stage III with advanced pannus, and a purulent conjunctivitis. In such instances the disease which was thought to be the most important factor was recorded.

Causes of Blindness	Blind in Both Eyes	Blind in One Eye
Trachoma	46	28
Onchocerciasis	39	10
Senile cataract	18	8
Couching for cataract	2	1
Congenital cataract	—	1
Trauma	1	17
Leucoma, phthisis, staphyloma:		
(*a*) Due to "bakwondoro"	5	10
(*b*) Due to smallpox	4	10
(*c*) Due to local eye disease	40	28
Glaucoma	5	1
Primary optic atrophy due to injections for sleeping sickness	4	—
Choroido-retinitis	3	3
Iridocyclitis and its results	1	5
Iridocyclitis due to cerebrospinal meningitis	2	—
Secondary optic atrophy due to cerebrospinal meningitis	1	—
Primary optic atrophy	—	1
High myopia	1	1
Retinal detachment	1	1
Old herpes ophthalmicus	1	—
Leprosy	—	2
Orbital tumours	—	3
	144	130

Trachoma is the commonest cause of blindness in the sample examined. It is believed to occur throughout Northern Nigeria, and the incidence increases as one travels northward towards the desert.

Onchocerciasis appears as the second commonest cause of blindness in my sample. This is probably not true of the whole of the Northern Provinces, for onchocerciasis causes a high incidence of blindness in localized areas only, and the tendency has been for me to survey areas where eye disease and blindness are common. However, it is a very serious cause of blindness in these areas. The lesions seen were similar to those described by Harold Ridley in the Gold Coast (*Brit. J. Ophthal.*, 1945, monograph, suppl. X).

Senile cataract is fairly common (18 out of 144 blind persons), but not as common as in Dr. Dodds's series (115 out of 356 blind persons). It is, however, probable that patients suffering from cataract attend the hospital in Lagos more readily than other blind persons because effective treatment is available. Couching for cataract is practised by itinerant Hausa Mallams in the Northern Provinces.

Trauma is a common cause of unilateral blindness.

I have seen no cases in which I could attribute blindness to vitamin deficiency. Although one patient with primary optic atrophy of unknown cause was seen, there was no evidence of pellagra as in the cases reported by Fitzgerald Moore from Southern Nigeria in 1938.

I am afraid that I have only seen a relatively small number of blind persons to date, but I felt that the differences between my findings and those of Dr. Dodds justified a further memorandum on the subject. In particular it is apparent that trachoma and onchocerciasis, which are relatively uncommon causes of blindness in Lagos, are important causes in Northern Nigeria.

I wish to thank Dr. S. L. A. Manuwa, the Inspector-General of Medical Services, Nigeria, for permission to publish this note.
—I am, etc.,

Jos, Nigeria. F. H. BUDDEN.

Diabetes and Pregnancy

SIR,—We have read with interest but little conviction the paper by Mr. H. H. Fouracre Barns and Dr. M. E. Morgans (May 17, p. 1058) in which, from a series of 24 diabetic pregnancies with four foetal deaths, they find justification for allowing such pregnancies to proceed to the onset of spontaneous labour. We were surprised to find no reference to the recent article by Drs. J. C. Pease and V. Smallpeice and Professor G. Gordon Lennon (June 9, 1951, p. 1296), in which the authors report 25 diabetic pregnancies with 23 live babies following termination at the 36th week of pregnancy. If any conclusion could be drawn from these very small series of cases it would be that the foetal loss rate following early termination is less than half that resulting from spontaneous labour. In fact the only conclusion which can safely be drawn from two such small series is that it is quite wrong to draw conclusions from inadequate data, and, if further proof were needed, it could readily be provided by taking random selections of 25 cases out of the 142 (not 123 as quoted) diabetic pregnancies reported by us in the *Transactions* of the 12th British Congress of Obstetricians and Gynaecologists.—We are, etc.,

King's College Hospital, Denmark Hill, S.E.5. WILFRID OAKLEY. JOHN PEEL.

SIR,—In the article "The Conduct of Pregnancy Complicated by Diabetes Mellitus" Mr. H. H. Fouracre Barns and Dr. M. E. Morgans (May 17, p. 1058) have shown very promising foetal salvage, although it was a small series of cases.

Premature termination of pregnancy has been advocated in order to protect the baby from the lethal effect of diabetes during the last few weeks of pregnancy, most probably due to excess of anterior pituitary hormone. Although birth injury contributes to a considerable extent mechanically, all being well this risk can be minimized or avoided by assessment in doubtful cases of the foetal pelvic relation prior to delivery.

The lethal effects of diabetes are mostly characterized by intrauterine foetal asphyxia and death, which are often

followed by spontaneous onset of premature labour, as shown in their case numbers 12, 14, and 18. In that case it would naturally be risky for the child if the pregnancy is allowed to continue until labour starts spontaneously. On the face of it the foetal salvage is, I think, due to induction of premature labour by high doses of stilboestrol alone, especially in the last few weeks, which has been interpreted by the authors as spontaneous onset of labour.

Both Smith, and Smith and White, suggested combined oestrogen and progesterone therapy in gradually increasing doses throughout the whole period of pregnancy on the hypothesis that both of these together act specifically in controlling the excess of anterior pituitary hormone. This seems to be more logical than stilboestrol alone.

The same difficulty of breast-feeding has been noticed by me in cases of mothers who undergo stilboestrol induction for intractable cases of toxaemia of pregnancy of all varieties, and I think it is due to a permanent inhibitory effect of oestrogen on the prolactin factor of anterior pituitary hormone.—I am, etc.,

Farnworth, near Bolton. B. BHATTACHARYA.

Needle Biopsy of Liver

SIR,—May I congratulate Dr. Richard Terry on his magnificent article (May 24, p. 1102), but as a humble anaesthetist may I remind him that it is not necessary to have deep anaesthesia in order to produce apnoea, and post-operative vomiting is nowadays an exception? It is a simple matter, by induction with a small dose of thiopentone, followed by one of the shorter-acting muscle relaxants ("scoline," "brevedil," or "flaxedil"), to give apnoea for from two to ten minutes, while the patient will remain only lightly anaesthetized and regain consciousness within a few minutes as if awakening from normal sleep.—I am, etc.,

London, W.1. FRANKIS EVANS.

Dermatitis after using "Pyrotenex"

SIR,—I was interested, as medical officer at a works making glass fibre, to read Dr. Cecil W. Ward's account of a case of dermatitis following the handling of a mineral-insulated cable (April 26, p. 905). Glass fibre from the cable was suggested as the cause. If the cable described is intended to refer to the mineral-insulated cable known to the trade as "pyroten*ax*," then I have the assurance of the manufacturers that the cable utilizes magnesium oxide as its insulant and that it contains no glass fibre.

There appears to be apprehension about the possible effect of glass fibre on the skin. In the factory where glass fibre is made and processed are workers who have handled the material without trouble for the 14 years since manufacture commenced. Workmen handling the glass fibre for the first time do frequently experience a skin irritation. This is a temporary phenomenon and usually clears up, in spite of continued contact, within a few days. The effects of this irritation when present can be minimized by the avoidance of tight sleeves, the use of a barrier cream, and the rinsing of the arms with running water before ordinary washing.—I am, etc.,

Pilkington Bros., Ltd., St. Helens. J. D. CAMERON.

Combination of Congenital Anomalies

SIR,—I am most grateful to Dr. C. Kerr McNeil (April 5, p. 762) for his comments on my article (March 1, p. 470). The association of hypertelorism with oral deformity is a most interesting and instructive feature. My observation that there was "no obvious anomaly of the eyes" was made in relation to the picture of partial arachnodactyly in my case. Arachnodactyly often has associated eye defects, such as congenital dislocation of the lens with trembling irides, as reported by Ormond and Williams (*Guy's Hosp. Rep.*, 1924, 74, 385). The high arched palate also is found in these cases of arachnodactyly. I could find no evidence of a cleft palate.

Dr. McNeil's observations are most instructive, and will stress the necessity for seeking congenital oral defects and other congenital abnormalities in cases showing evidence of hypertelorism.—I am, etc.,

Johannesburg, South Africa. I. KESSEL.

Adrenal Cortical Function at Death

SIR,—I was interested to read Dr. Paul B. Jennings's article (May 17, p. 1055). My findings, so far as they go, support Dr. Jennings's contention that adrenal cortical exhaustion does not occur even in fatal cases, and that secretory activity of this gland continues up to the very moment of death.

Diagnosis	Eosinophil Count	
	Hours Prior to Death	Cells per c.mm.
Head injury. Trephining of skull. Bronchopneumonia	24	0
Nephrectomy. Pyelonephritis. Uraemia	15	0
Carcinoma of liver. Intestinal obstruction	6	0
Hypernephroma. Metastases in lungs, liver, and both adrenals	7	10

All these cases had had eosinophils at some time in the circulation

It is not justifiable, however, because there is a high rate of adrenal cortical secretion at this time, to assume that adrenal cortical substances will prove therapeutically ineffective in terminal states. Crassweller and his colleagues (*British Medical Journal*, 1950, 2, 242 and 977) have shown that cortisone is of value in the treatment of burn shock in normal subjects and in non-adrenalectomized mice.

Surely adrenal cortical insufficiency may be either absolute—as occurs, for instance, in Addison's disease—or relative, where the adrenal cortex secretes maximally in response to the stress; but the latter is of such magnitude that the tissue demand for the adrenal cortical hormone is only partially satisfied. Relative insufficiency may exist even in the presence of a high rate of adrenal cortical secretion, and the administration of adrenal cortical extract in these circumstances is not an unreasonable therapeutic procedure.—I am, etc.,

London, N.W.3. J. F. BUCHAN.

Cowpox

SIR,—Cowpox is of sufficient rarity to evoke interest when it occurs, as it does sporadically, in a rural community. Three such outbreaks have occurred in my practice during the past three years. In one, three adult members of one family were affected, and, in the second, one adult in a remote district. The diagnosis of these was confirmed by Professor Downie (University of Liverpool), who reported on the former: "From this swab we isolated a typical strain of cowpox virus."

A further case presented itself 10 days ago in a farmer (a relative of the three adults mentioned above, living on an adjacent farm). The lesion on the wrist was typical and presented no difficulty in diagnosis; there was lymphangitis of the forearm, enlarged and tender epitrochlear and axillary glands, and his temperature was 102° F. (39° C.).

From the general practitioner's point of view it is interesting to note the remarkable results of treatment with chloramphenicol, for overnight the temperature became normal, the lymphangitis resolved, and the glands were less tender. It would be interesting to know if chloramphenicol has been used in the treatment of smallpox, and, if so, if it has proved as strikingly successful as in its less virulent related form.—I am, etc.,

Ruthin. TREVOR HUGHES.

Accidental Generalized Vaccinia

SIR,—The report of a case of generalized vaccinia contracted by an eczematous infant published by Drs. O. A. Finn, J. C. Dick, and J. S. Stevenson (May 17, p. 1067), was of particular interest to us. Last October a similar case, a child aged 11 months, was admitted to this hospital. The mother and other members of the family had recently been

vaccinated prior to emigration. Our patient's vaccinia commenced on the eczematous areas and was generalized on admission. Virus studies confirmed the diagnosis.

"Aureomycin" had no effect on the viraemia. On the fifth day the temperature had risen steadily to 105° F. (40.5° C.), the pulse rate was extremely rapid, and the child's general condition was very grave. A highly concentrated post-vaccinial gamma globulin obtained from the Public Health Laboratory, Colindale, was now given. Within 12 hours there was for the first time a remission of the temperature, a slowing of the pulse rate, and an improvement in the general condition. This remission was not fully maintained, but ultimately the child survived. We make no claim for this serum, which was given so late and in only one case. In fact we used the only sample obtainable. The mortality in this variety of Kaposi's varicelliform eruption is so high, however, that we suggest a trial of the immediate use of such a serum in future cases.—We are, etc.,

J. MERVYN THOMAS.
Chelmsford. P. J. FEENY.

Mumps with Involvement of Lacrimal Glands

SIR,—I was interested in the memorandum by Drs. J. F. Galpine and J. Walkowski (May 17, p. 1069) because I was unaware of the rarity of the condition. During the past four years in a general practice of some 4,000 patients I have had one such case. The number of cases of mumps attended during the same period was 153. The case with lacrimal gland involvement was that of a woman of 22 years who developed typical mumps parotitis on January 13, 1949, an epidemic being present in the area at the time. Both lacrimal glands also became swollen on this date, but not to the degree of Galpine and Walkowski's case. The patient looked as if she had a hazel nut under the outer side of both upper lids. The attack was not a severe one, and the dacroadenitis cleared up quickly.—I am, etc.,

Cirencester. R. E. HOPE SIMPSON.

Laryngeal Vertigo

SIR,—Recent contributions to the *British Medical Journal* (e.g., March 22, p. 653) on the subject of laryngeal vertigo and laryngeal epilepsy have emphasized the fact that the modern literature of this subject is extremely scanty and our real knowledge of the syndrome is far from complete. It therefore seems desirable that cases in this category should be briefly placed on record.

A foundry manager, aged 44 years, complained of attacks of giddiness from June, 1951, until February, 1952. During 1951 he had a few isolated attacks, but in January, 1952, he had several attacks every week, and on occasion several attacks in one day. His description of his sensation during an attack is as follows. He experiences a tickling sensation in the back of his throat and gives a short cough which is immediately followed by a feeling of giddiness. He has never lost consciousness or fallen down in an attack, but has always had to cling to something for support. He feels "as though he were drunk," but does not experience the sensation of objects revolving round him. The attacks have varied in duration from a few seconds to five minutes. He himself attributes the onset of an attack to the inhalation of fumes from iron castings; the inhalation of tobacco smoke appears to produce the same results. Detailed clinical examination did not reveal any abnormality in the various systems of his body, except for a slight erythema of the post-pharyngeal wall.

It is interesting that the initiation of the syndrome, by a tickling sensation at the back of the throat followed by a short cough, conforms exactly to the symptoms originally described by Charcot under the heading of laryngeal vertigo. An additional point is that the patient develops a modified form of vertigo without the subsequent occurrence of coma. It is therefore both logical and historically accurate to apply to this patient's illness the label "Laryngeal Vertigo of Charcot."

The exciting cause of attacks of this nature is usually laryngeal irritation, in the present case produced by the inhalation of fumes from iron castings and also from tobacco smoke.

His illness, therefore, clearly raises points of legal importance in industrial medicine, as involuntary loss of balance in a man engaged in the process of iron casting might be attended by a serious or fatal accident.—I am, etc.,

Arbroath, Angus. HERBERT CLARK.

Physical Therapy versus Psychotherapy

SIR,—Whilst I am in agreement with the use of physical methods in psychiatric practice—having used these in my own practice for the past 10 years—I cannot agree with the somewhat facile and dogmatic assumptions made by Dr. H. M. Flanagan (May 24, p. 1132). If in his experience such methods are successfully superseding psychotherapy he is more than a shade luckier than many of us. A more equitable and considered statement would be that physical and psychological methods are now being used where before very little could be done for mental sufferers. Every practising psychiatrist has had successes with physical methods, but, alas, many are the disappointments following our first high hopes. Electronarcosis, electroshock, leucotomy, prolonged narcosis, insulin coma, and others—who, amongst the original sanguine enthusiasts, is now prepared to shout them from the housetops?

As to Dr. Flanagan's daring and cocksure assertion that mental disease "depends upon physical deficiencies," only the words "wishful fantasy" occur to me. But then, some of us prefer the rigid autocracy of the switch and the test-tube to the more pliable democracy of psychic theories where mental disturbance is concerned. And each of us has his own conscious and unconscious motives for such preference, motives in which ethics, morals, and religious background play no inconsiderable part.—I am, etc.,

Kingswinford, Staffs. W. A. O'CONNOR.

Oesophagitis

SIR,—Having had personal experience of oesophagitis for the past 18 months, I should like to congratulate Dr. J. B. Harman on the accuracy of his description (May 3, p. 941) of this complaint, of which very little appears to be usually known.

The attacks, which invariably occur at night—about two and a half hours after sleeping, in my experience—vary considerably in intensity, the more severe form usually lasting at least an hour, followed by a sense of soreness and nausea which continues for the rest of the night and much of the succeeding days. These acute attacks are well described by Dr. Harman as being central (retrosternal) in location, with a sensation of "wind, food stuck, pressing, or burning" (or all of them), and radiating later to the sides and back. It is a feeling of being in a vice, and thoracic breathing is often quite difficult and painful, though diaphragmatic breathing remains comparatively easy. The more chronic form, which may last many hours after the acute attack, is like constant pressure applied to the sternum.

I am surprised that the article does not refer to what I have personally found to be the most persistent and unpleasant symptom of all—namely, constant nausea.

The symptoms are quite distinct from dyspepsia, with which they are commonly confused, and neither diet, alkalis, nor antispasmodics appear to have much influence on them. The absence of positive evidence by radiology and oesophagoscopy, unless on repeated occasions, cannot be taken as refuting the diagnosis.

There is a delightful touch about Dr. Harman's concluding remarks, that, as the attacks are likely to get gradually worse but are not likely to have fatal consequences, the patient should be advised to carry on as he is doing until he is sufficiently miserable to prefer the risk of a major operation!—I am, etc.,

Beckenham, Kent. HAROLD BALME.

SIR,—Speaking of oesophagitis, your readers may like to hear what the acute form feels like to a subject of it, especially as it seems rather rare.

It attacked me suddenly when about 35 years of age. There was pain in the fauces at both sides, with dysphagia.

It progressed steadily downwards, with pain referred to the middle line in front. The sensation marched, as it were, right down to the lower end of the sternum, and then faded away, as I had fervently hoped it would. This took about four days, and for more than two not even saliva could be swallowed, though there seemed to be no excessive secretion of mucus. Considerable dehydration must have been produced, for a pint of water was quickly absorbed from the rectum. The pharynx felt normal again before the process had reached the extent of its travel. There was, of course, no oesophagoscopy, and one can only surmise that in appearance it would have looked like erysipelas. The stomach was not disturbed.—I am, etc.,

Doncaster. W. R. WILSON.

Torsion of Fallopian Tube during Pregnancy

SIR,—The memorandum by Drs. N. P. Ellison and J. S. W. Chambers (March 29, p. 694) prompts me to place upon record the following case.

A mother of two children, aged 32, was seen on October 18 at the Bignold Hospital, to which she had been admitted two days previously. Her first two pregnancies were normal. Her last menstrual period was on July 23, and the pregnancy followed a normal course until the day before admission, when, following a violent effort while washing blankets, she was seized with severe lower abdominal pain and backache, radiating up to the right costal margin. There was no bleeding and no pyrexia, but pain had persisted in spite of rest in bed, and when I saw her she looked flushed and ill. The uterus showed the characters of a three-months pregnancy, and above, behind, and to the right was a markedly tender mass of almost the same size. In view of a recent experience of tubal torsion unassociated with pregnancy, a tentative diagnosis was made of torsion of the right appendage complicating pregnancy, and a few hours later at operation I found that this was correct. The right tube and ovary were involved in a torsion two and a half times in a clockwise direction around a point about the middle of the tube, and both the ovary and the distal part of the tube were black and gangrenous. Removal of the appendage was completed without difficulty and the pregnancy continued uneventfully to term, when a live child was born. The opposite tube and ovary appeared healthy, but it was noted that a considerable length of the fimbrial end of the tube lay free beyond the point of insertion of the infundibulo-pelvic ligament. It seems probable that this fact predisposed the tube to torsion and that the accident was precipitated by violent physical effort.

The question of appendicitis in this case presented no difficulty, since the appendix had been removed some years previously.—I am, etc.,

Worcester. J. A. CHALMERS.

Gout and Insulin Hypoglycaemia

SIR,—Three patients with acute gout (one with chronic tophaceous gout as well) treated with mild insulin hypoglycaemia recovered from the acute phase in three to twelve days. Two had histories of one and two attacks yearly, for eight to fifteen years, each attack lasting between two to six months. The third had his first attack of gout in early October, 1951, when treatment was begun.

Marked relief from pain was noted by all patients within 4 to 24 hours after the first injection. Objectively, the swelling and violaceous discoloration showed improvement within 18 to 48 hours. Of interest is the rapid restitution of the initially high E.S.R. to nearly normal levels by the third to twelfth day, while the blood uric acid level remained constant. The one patient with the chronic tophaceous stiff finger regained his power to flex it by the sixth day. All of his tophi had perceptibly softened and diminished in size. Comparative radiographs of the tophaceous patient on the eleventh day revealed anabolic activity in both cystic and osteoporotic bone.

The method of treatment was similar to that previously described in the treatment of rheumatoid arthritis (*J. Amer. med. Ass.*, 1951, **145**, 842), with the following changes: (*a*) in the second week and thereafter injections were given three times weekly on alternate days, and (*b*) ascorbic acid, 4 g. daily, was given in order to prevent adrenal cortex exhaustion as well as to ensure possible precursors for cortical hormones. Regular insulin (25–70 units) was injected intramuscularly into patients, who had fasted overnight, in the medical clinic. The dosage was so adjusted as to produce a mild hypoglycaemic reaction (mild sweat) within one and a half to two hours, which was at once counteracted by orange juice (glucose and potassium), meat or cheese sandwiches (amino-acids), and milk. Further feeding at home prevented additional reactions. For the first week injections were given on two successive days, then omitted on the third day, and then followed by two successive days of injection. However, this schedule was varied, but the mild reaction and intervening rest days were adhered to, because experience has demonstrated that the hypothalamus is easily exhausted as a homoeostatic organ.

The exact hormonal mechanisms involved are unknown. Further studies are being conducted.

It is hoped this use of insulin in the treatment of gout will be of value to others.—I am, etc.,

Oakland California. HERBERT A. WEITZNER.

Cricket

SIR,—The Law has challenged Medicine once again, but this time the contest is on the cricket field. The Law Society Cricket Club has issued a challenge to the B.M.A. to a match at Hurlingham, London, on Sunday, July 5, 1953, at 11.30 a.m. This challenge has been provisionally accepted by Council, and I have been asked to raise a side. This preliminary letter is published at this early date to draw the attention of members of the Association to this match, and in the hope that any members who have club or county experience will get in touch with me at Herons Lea, Wadhurst, Sussex, giving their "qualifications" on the cricket field and their potential capabilities. The Association should be able to get together a good side to meet and overcome this challenge and to inaugurate what may well be a most interesting and, may I say, amusing annual interlude.—I am, etc.,

Wadhurst. R. PROSPER LISTON.

Bequests to Nationalized Hospitals

SIR,—May I draw attention to a curious omission from the article by your medico-legal correspondent (May 31, p. 1200) on bequests to nationalized hospitals?

In describing the case of the will of Lady Bland-Sutton, he fails to mention that a further appeal to the House of Lords resulted in a confirmation of the judgment that the Middlesex Hospital had become nationalized and passed into public ownership, but also determined that the Royal College of Surgeons was a charity. Lady Bland-Sutton's attempt "to provide for what was to happen if the hospital concerned was nationalized" was, unlike that of John Edward Frere, completely successful, and the Royal College of Surgeons will receive the Trust Fund created from the residue of Lady Bland-Sutton's estate.

The Royal College of Surgeons of England is a charity, is entirely free from State control, and can accept gifts, for medical research and education, which can be administered by its council without interference, and I feel sure that your medico-legal correspondent would not wish to leave your readers with any contrary impression.—I am, etc.,

Lincoln's Inn Fields, W.C.2. KENNEDY CASSELS, Secretary, Royal College of Surgeons.

POINTS FROM LETTERS

Foot and Mouth

Dr. P. STUART SMITH (Ombersley, near Droitwich) writes: It seems to me that it is high time to put an end to the complacent attitude of Ministers, farmers, veterinary surgeons, and the general public to the slaughter of thousands of our best sheep, cattle, and pigs in an attempt to control the spread of foot and mouth disease. . . . I feel that insufficient effort appears to have been directed to finding a cure or preventive for this dread disease. More than £1,000,000 has been paid out this year in compensation, but how much, I wonder, has been paid for research?

Obituary

LAURENCE KILROE, M.D.

Dr. Alfred Cox writes: May I add a few words to the affectionate tributes (May 31, p. 1197) paid to my old friend? As Medical Secretary of the B.M.A. I knew him as one of the most efficient of our division secretaries. The way he handled Association affairs and his colleagues gained my respect and admiration. But I got to know the man more intimately when he became my travelling companion on the journeys between Winnipeg and Victoria in 1930. I then realized what a versatile, accomplished, and lovable man he was, and his sense of humour made him quite irresistible. We met only very occasionally after my retirement, but our meetings were always a joy to me. I shall always cherish my memories of him.

Mr. LEONARD AUSTIN HARWOOD, who died at his home at Normandy, Surrey, on May 13 at the age of 65, was born on August 31, 1886, and received his professional training at the Royal Dental Hospital, London, and at the Westminster Hospital, to which he won an entrance scholarship. He took the diploma of L.D.S. of the Royal College of Surgeons of England in 1908, and qualified in medicine by taking the London Conjoint diplomas three years later. After holding the posts of demonstrator in dental surgery and tutor at the Royal Dental Hospital he was appointed medical superintendent and dental surgeon to the dental department at University College Hospital. Another appointment he held was that of dental surgeon to the Royal Cancer Hospital. He was a past-president of the Chelsea Clinical Society. A member of the Territorial Army since its formation, Mr. Harwood was awarded the Territorial Decoration in 1927 for his services, and retired in 1949 with the rank of colonel. Mr. Harwood leaves a widow, Dr. L. Fanny Harwood, who also has both dental and medical qualifications, and two daughters and one son.

Dr. Russell V. Steele writes: The passing of Leonard Harwood will have come as a great shock to all who had the privilege of knowing him. I could count him as one of my best friends, a friendship which began in 1906, when we were both members of the old R.A.M.C. Volunteers (London Company). Harwood carried on when the Territorial Army came into being, and rendered invaluable service in the war of 1914–18 with the 84th (2nd City of London) field ambulance. Not only was he skilled in medicine and a successful dental practitioner, he was also a good soldier and administrator, becoming eventually assistant director of medical services, London District. In spite of the fact that his health was undermined in Macedonia, he was abroad again in the last war, this time in West Africa. A true and loyal friend and one of the kindest of men, he will always be remembered with pride and affection by his old comrades of the 84th field ambulance.

The death of Dr. JOHN HUDSON CLIFFORD on May 16, at his home in Finchley, at the age of 59, is a grief to a large circle of friends and patients, but it was not unexpected, as for years he had been sacrificing his health for his work, in spite of warnings from many of his medical friends. Dr. Clifford served with the Royal Engineers in Mesopotamia in the war of 1914–18, and on his return from active service he studied medicine at the University of Aberdeen, graduating M.B., Ch.B., in 1923. After holding various appointments he settled in Finchley over 20 years ago, and rapidly built up a large and widespread practice. He also served on the local borough council, where his sound judgment and professional experience were deeply appreciated. Dr. Clifford will be sadly missed by a wide circle of patients, who looked upon him as a friend, his advice frequently being sought on matters other than medical. Deep sympathy will be felt for his widow and for his two married daughters and his son, who is following his father's profession.—McN. L.

Colonel DOUGLAS CRELLIN, who died at Harrogate on May 15 at the age of 62, was born at Douglas, Isle of Man, on March 4, 1890, the son of Mr. John Crellin. He was educated at Douglas and in London, and then at St. John's College, Cambridge, and St. Bartholomew's Hospital, qualifying M.R.C.S., L.R.C.P. in 1916. He entered the R.A.M.C. as a regular officer immediately after qualification and within a few months was in France, serving in the war of 1914–18. In 1918 he was awarded the Military Cross for gallantry at Passchendaele. After the signing of the armistice he served with the army of occupation at Bonn in Germany, and also in France. In 1938 he went to Egypt and subsequently to Palestine and Greece. During the last war he served in Iraq, India, and at home, and was mentioned in dispatches in 1940, 1942, and in 1943. He retired from the service in 1947 with the rank of colonel. He is survived by his widow.

Medical Notes in Parliament

Poisonous Chemicals in Agriculture

When the Agriculture (Poisonous Substances) Bill was reported in the House of Lords on May 27, Lord DOUGLAS OF BARLOCH proposed a new clause to ensure that a manufacturer would be under a legal obligation to consider the nature of the substances which he offered for sale, and would have an obligation to deliver particulars to the Ministry of Agriculture so that they could make an order for regulating the means and the manner by which the substance was used.

Lord CARRINGTON, for the Ministry of Agriculture, did not think the amendment would be suitable. If it were accepted the public would think that substances notified to the Minister had been approved by him. Any idea of approval by the Minister was not acceptable to the Government. It was the manufacturer's job to see that the properties of these substances were known, and his duty to carry out necessary tests and trials. He noted that the word poisonous, which was introduced into the amendment, was not used or defined in the Bill as it stood. The Zuckerman Working Party had considered the problem, but had not recommended that statutory requirements should be imposed on suppliers in the way Lord Douglas proposed. The Ministry received prior information about most of the substances which it was proposed to put on the market. The principle that there should be prior information about new toxic products had been fully accepted by the manufacturers.

Lord DOUGLAS OF BARLOCH said that, although Lord Carrington contended that in practice the Ministry was informed, he had never explained the regrettable circumstances connected with the use of D.N.C., which was a well-known poison about which the Ministry was not told. Lord CARRINGTON said that was why the Government had introduced the Bill.

Lord DOUGLAS'S proposed amendment was then negatived and the report stage concluded.

Corneal Grafting Bill

In the House of Lords on May 27 Lord HADEN-GUEST moved the Second Reading of the Corneal Grafting Bill. He said it had been supported in the House of Commons by Members of all parties, including two Ministers of Health. Blindness from opacity of the cornea could be cured and the sight restored if the cornea from another human eye could be grafted on to the blind eye. Such a use had already been made of eyes of the dead in France, Spain, and South Africa.

Lord ONSLOW, for the Government, said he was wholeheartedly in support of the Bill.

Lord WEBB-JOHNSON said the need for the Bill was great, but he believed it would diminish. The need was even greater in those Colonies which depended on Britain for guidance in medical matters and often for medical service. In the Middle East thousands of cases of trachoma led to complete incapacity of the front window of the eye, which was remedied by grafting in a clear window.

Lord LLEWELLIN doubted the wisdom of the use of the phrase "for therapeutic purposes" in Clause I dealing with the bequest of a person's eyes during his last illness.

Lord HADEN-GUEST said the words challenged by Lord Llewellin had been carefully considered by the Ministry of Health, but he would look into the matter to see whether any adjustment was necessary. He hoped that the Bill would give a lead to the Commonwealth.

The Bill was then unanimously read a second time.

Doctors' Pay

On May 29 Dr. A. D. D. BROUGHTON inquired what progress had been made in the plans for a more equitable distribution of general medical practitioners' pay, and whether the forthcoming new scheme would be submitted to Parliament for approval. Mr. IAIN MACLEOD replied that the working party set up to agree a new method of distribution had completed its report. Copies would be available on June 5. Any necessary amending regulations would be laid before Parliament in the ordinary way.

In reply to a further question by Dr. Broughton Mr. Macleod said that further opportunities were available for the Opposition to debate the matter. He would consider publishing evidence of the distribution of doctors' payments at the time when the Working Party began its report or when the Danckwerts investigation started.

Cancer Cure

Mr. PETER FREEMAN, on May 29, asked if the Minister of Health could make a statement on the results of the inquiry into the Rees Evans cancer cure.

Mr. IAIN MACLEOD said a committee had been appointed by his predecessor in October, 1950, consisting of Sir Robert Robinson as chairman, Sir Ernest Rock Carling, Sir Alexander Fleming, and Sir Harold Himsworth, to consider Mr. Rees Evans's claims to have discovered a treatment for cancer, and to advise whether they warranted further investigation, and if so the way in which any investigation should proceed. The report had now been received. In the normal way he would have proposed to publish it, but, as it contained information supplied to the committee in confidence by Mr. Rees Evans and by patients and their relatives, he could not do so. He could, however, say that the committee advised him that the claims made did not warrant further investigation. He had accepted that advice, and would circulate a fuller statement of the committee's conclusions in the official report.

The statement is as follows:

The committee examined the histories of British and American patients treated by Mr. Rees Evans, and also investigated the materials used by him in his work, as well as receiving oral and written evidence from him. It did not examine patients under treatment, since it considered that in most forms of cancer assessment of the results of treatment is not possible until the patient has remained well for at least five years after treatment has ended, and also since the technical details of applying any particular treatment are irrelevant to the assessment of its value in treating cancer.

Examination of the histories of 22 British patients treated by Mr. Rees Evans between 1931 and 1945 who could be traced from 34 names supplied led the committee to the following conclusions:

Insufficient information for diagnosis	5
Judged not to have suffered from cancer	7
No convincing evidence of cancer at time of treatment	3
Dead from or seriously ill from recurrence of cancer after treatment	2
Rodent ulcer	5

Inquiries were not pursued in the cases of rodent ulcer, on the grounds that it is a form of skin cancer of slight malignancy; that it has been known for many decades that it can be successfully treated by several methods which remove the locally affected tissue; and that evidence of success in healing rodent ulcers throws no light on whether the same method will be useful in the treatment of cancers in general.

Examination of the histories of 16 American cases treated by Mr. Rees Evans in 1949–50 was also made, and the condition of these patients in July, 1951, was as follows:

Dead from cancer	8
Seriously ill from cancer	1
No convincing evidence of cancer	2
Condition doubtful	1
No recurrence of cancer, but also treated surgically or with *x* rays	2
Rodent ulcer	2

On its inquiries into these British and American cases the committee came to the conclusion that they provided no evidence that the Rees Evans treatment of cancer is of any value, though it may have an effect on rodent ulcers.

Samples of the materials used by Mr. Rees Evans in treatment were analysed, and tested in experiments on animals. The committee was advised by a leading expert that the results obtained did not provide any indication for recommending further experiments.

On the basis of its inquiries into case histories and into the materials used, the committee has accordingly advised that the claims made by Mr. Rees Evans to have discovered a treatment for cancer do not warrant further investigation.

After Mr. Macleod's oral statement, Mr. FREEMAN asked whether the Ministry did not think the time ripe for a full and independent inquiry into the cause of cancer. He said that in this country the disease was responsible for the largest percentage of deaths of any country in the world. Mr. MACLEOD said Mr. Bevan had appointed the committee to report whether there was anything to investigate. That committee was unequalled in its standing. It had advised him in the sense he had told the House.

Mr. ANEURIN BEVAN asked whether Mr. Macleod agreed that giving such publicity to claims before they had been properly investigated was peculiarly offensive and hurtful. All that had been done could have been done by sending a letter to the Ministry of Health without arousing hopes of sick people unnecessarily. Mr. MACLEOD said he entirely agreed with all Mr. Bevan said.

Mr. SOMERVILLE HASTINGS asked whether there was not a higher proportion of cures of cancer to-day than at any previous time. Mr. FREEMAN asked whether the committee was not entirely medical, and whether there was a case for investigation along other lines, as the problem might also be industrial. Mr. MACLEOD said another committee could not be set up with anything like the same prestige.

Mr. BEVAN asked whether Mr. Freeman was not doing a great disservice in attempting to suggest that the claims had not been properly investigated. That would lead a number of people to believe that further investigation was necessary when, as a matter of fact, the claims in the first instance were without foundation.

Cremation Bill

The Cremation Bill passed through the report stage on May 23. On the motion that it be read a third time, Dr. A. D. D. BROUGHTON drew attention to Clause 3 (1) providing that the Home Secretary could prescribe the fees for the issue of any medical certificate required under the Cremation Act, 1902. He assumed the Ministry would consult representatives of the medical profession, and urged that the figure should be fair and reasonable. Doctors who filled in medical certificates for cremation undertook a heavy responsibility. It might be worth while for the Ministry to prescribe two fees, the higher for a second certificate issued by a doctor with at least five years' experience.

Sir HUGH LUCAS-TOOTH said the fees would be maximum fees. It would be open to a doctor to charge a lower fee. Discussions with the doctors had started.

The Bill was read a third time.

Cod-liver Oil for Tuberculous Patients

On May 29 Dr. SANTO JEGER asked the Minister of Health whether it was on his instructions that doctors were receiving communications from executive councils proposing surcharges in cases where cod-liver oil and malt extract had been prescribed in the treatment of tuberculosis. Mr. IAIN MACLEOD said there might be some misapprehension on this subject, on which he had issued no instructions. The Definition of Drugs Subcommittee advised that when cod-liver oil and malt was used for the treatment of tuberculosis it should be regarded as a drug. Its report also said that a doctor must be prepared to justify the ordering of the preparation as requisite for the treatment of his patient. He proposed to bring the report to the attention of executive councils and general practitioners again.

Unused Beds.—On December 31, 1951, the number of hospital beds in England and Wales unoccupied through lack of staff was 32,668, or about one-fifteenth of the total number of beds.

Cathode-ray Costs.—The glass bulb for a 15-inch television cathode-ray tube costs £2, and the remaining materials about 7s. 6d.

Assistants in Practice.—The numbers of assistants employed by general medical practitioners in the National Health Service at March 31, 1950, and at the end of 1951 were 2,088 and 1,998 respectively.

Patient Costs.—A publication showing the patient costs in individual hospitals in England and Wales for the year ending March 31, 1951, is to be issued about the middle of June.

Medico-Legal

MENTAL CONDITION OF WITNESSES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On June 13, 1951, the Court of Criminal Appeal[1] dismissed the appeal of Dr. Sumatapalage Reginald Gunewardene from his conviction at the Central Criminal Court for manslaughter. He was tried together with Alice Hanson, who was convicted of the manslaughter of a single woman aged 27 by means of an illegal operation. Dr. Gunewardene was found to be an accessory before the fact and so a principal in the second degree, and was sentenced to three years' imprisonment.

The prosecution's case against him was that he drove the deceased woman, who was then pregnant, to Alice Hanson's house in order that an operation to procure an abortion should be performed, that after the operation he collected her from the house and drove her home again, that later he attended her at the house of one of his patients, and caused her to be taken to hospital. She died on the way to hospital of general septicaemia, thirty-six hours after the operation. Dr. Gunewardene's defence was that he had attended the woman for what he thought to be a normal miscarriage, and had had nothing to do with the operation.

The most important ground of appeal was that the judge at the Old Bailey had excluded the evidence of a doctor whom it was sought to call on Dr. Gunewardene's behalf to testify to the mental condition of a witness for the prosecution: this witness had given evidence highly prejudicial to Dr. Gunewardene, and his mental condition was likely to affect his truthfulness. The Court of Criminal Appeal, after reviewing the law on the question, upheld the trial judge's refusal. The position is that, while the defence can call witnesses to say that they believe, from their knowledge of a particular prosecution witness, that he is unworthy of credit upon his oath, they cannot be called to give the reasons for their belief: and it was just this the defence was seeking to do.

If a defence witness is called to say that he believes that a prosecution witness is unworthy of credit he can, however, be asked the reasons for his belief in cross-examination, and his answers cannot be contradicted, though they may of course be not believed.

[1] [1951] Weekly Notes, p. 357.

Universities and Colleges

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College, held on May 8, with Sir Cecil Wakeley, President, in the chair, Mr. E. H. Shaw, Dr. S. A. Henry, Mr. V. B. Green-Armytage, Sir William Kelsey Fry, and Professor John Kirk were admitted to the Fellowship, having been elected as practitioners of twenty years' standing. Mr. G. T. W. Cashell was admitted to the Fellowship *ad eundem*.

The Jacksonian prize was presented to Mr. Rodney Smith (St. George's) and an honorarium and a certificate of honourable mention to Mr. G. O. Jelly (Manchester). The John Hunter medal and triennial prize were presented to Dr. Cuthbert Dukes. The Begley prize was presented to Miss J. R. Carlton Jones (Charing Cross).

Sir Cecil Wakeley was reappointed representative of the College on the General Medical Council.

Sir Ernest Finch was appointed the Thomas Vicary Lecturer for 1953. The award of the first Lister award in ophthalmology and travelling scholarship to Dr. M. E. Langham was reported.

The Council accepted an offer from Lord Webb-Johnson to present the design of a College tie and the first consignment of ties.

Diplomas of Membership were presented to Y. A. Motala and to the 149 successful candidates whose names were printed in the report of the meeting of the Royal College of Physicians of London in the *Journal* of May 3 (p. 979).

Diplomas were granted, jointly with the Royal College of Physicians of London, as follows:

DIPLOMA IN ANAESTHETICS.—A. E. Hocking, W. N. Wild.

DIPLOMA IN CHILD HEALTH.—L. I. Phillips.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—B. Devlin, A. K. Mitra, D. M. Montgomery.

The following hospitals were recognized under paragraph 23 of the Fellowship regulations: King George VI Hospital, Nairobi, resident surgical officer and two senior house-surgeons (until March 31, 1953), for one year. Mulago Hospital, Uganda, three senior residents in surgery, for one year. Victoria Hospital, Burnley, surgical registrar, senior house officer, two house-surgeons, all for six months (decennial revision). East Suffolk and Ipswich Hospital, *additional recognition*, senior house officer to fracture and orthopaedic department, for six months. Royal Lancaster Infirmary, first and second house-surgeons, two orthopaedic house-surgeons, all for six months (decennial revision). Brook General Hospital, London, two house-surgeons in thoracic surgery unit, for six months; two house-surgeons in neurosurgery unit, for six months. Lewisham Hospital, *additional recognition*, senior house officer in orthopaedic and traumatic department, for six months. St. Alfege's Hospital, Greenwich, *additional recognition*, third house-surgeon, for six months. Reedyford Hospital, Nelson, surgical registrar, for six months. Boundary Park General Hospital, Oldham, *additional recognition*, house-surgeon, general, for six months. Oldham Royal Infirmary, *additional recognition*, two house-surgeons, general, for six months.

UNIVERSITY OF OXFORD

Dr. E. M. Vaughan-Williams has been appointed University Demonstrator in Pharmacology from October 1, 1952, to September 30, 1957.

Anthony Clifford Allison, D.Phil. (Merton College), has been elected to a Staines Medical Research Fellowship at Exeter College, as from October 1.

UNIVERSITY OF CAMBRIDGE

In Congregation on May 24 the degree of M.Chir. was conferred on Thomas Fenwick.

UNIVERSITY OF LONDON

Percy Cyril Claude Garnham, M.D., D.P.H., has been appointed to the University Chair of Medical Protozoology tenable at the London School of Hygiene and Tropical Medicine, from October 1.

John Archibald Browne Gray, M.B., B.Chir., of the National Institute for Medical Research, has been appointed to the University Readership in Physiology tenable at University College, from October 1.

The following candidates have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part I:* W. P. Gurassa, J. L. J. Lumey, A. C. Parkin, F. G. Tait.

POSTGRADUATE DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*With Special Knowledge of Mental Diseases (Psychiatry):* J. M. Cuthill, B. V. Earle, F. J. Fish, Hildegarde C. Fisher, M. H. Friedman, J. L. Gibbons, R. C. Gledhill, J. Guild, Mary L. Hare, A. Hordern, A. G. Hucker, J. G. Jesson, Moyra S. M. Kemp, Anne K. Kirkland, N. P. Lancaster, F. Letemendia, C. S. Lindsay, Janet N. McCulloch, D. G. McLachlan, J. Marshall, D. W. Moynagh, Dorothea M. Norman-Jones, W. Pappenheim, R. H. Park, J. M. K. Rehmany, W. J. B. Rogers, D. J. Salfield, W. K. Schnarr, J. R. Smythies, J. B. Stanton, S. Stein, K. F. Weeks, D. J. West. *With Special Knowledge of Mental Deficiency:* J. B. Jeffries, M. P. Nelson, E. W. Shepherd. *Part A only:* I. C. Church, Stefanie Felsenburg, Marjorie A. Morgan, B. S. Stephen.

Professor R. V. Christie and Professor W. G. Barnard have been appointed members of the Senate for the period 1952–6, representing the Faculty of Medicine and the General Medical Schools respectively.

The following have been appointed or nominated for appointment or reappointment as representatives of the University on the governing bodies indicated in parentheses: Professor S. J. Cowell and Professor Esther M. Killick (King's College of Household and Social Science); Professor J. M. Mackintosh (Slough Industrial Health Service Ltd., Council of Management).

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. George's Hospital Medical School,* Mr. H. E. Blake (Surgery). *Postgraduate Medical School of London,* Dr. G. MacG. Bull and Dr. C. L. Cope (Medicine). *St. Mary's Hospital Medical School,* Mr. J. C. Goligher (Surgery). *London Hospital Medical College,* Dr. R. A. Henson (Medicine); Dr. A. M. Horsnell (Dental Surgery). *Middlesex Hospital Medical School,* Mr. O. V. Lloyd-Davies (Surgery). *University College Hospital Medical School,* Mr. W. R. Merrington (Surgery). *Charing Cross Hospital Medical School,* Dr. R. M. Patterson (Radiology). *St. Bartholomew's Hospital Medical College,* Mr. C. Naunton Morgan (Surgery). *Royal Free Hospital School of Medicine,* Dr. Kathleen M. Robinson (Obstetrics and Gynaecology); Dr. A. G. Stansfeld (Pathology). *London School of Hygiene and Tropical Medicine,* Dr. D. A. Smith (Hygiene and Public Health—Human Nutrition). *Institute of Ophthalmology,* Dr. L. C. Thomson (Physiology). *Institute of Psychiatry,* Dr. W. Warren (Mental Diseases). Probationary recognition as teachers of the University has been granted, for two years from April, 1952, to the following: *Charing Cross Hospital Medical School,* Dr. W. E. D. Evans (Pathology). *Middlesex Hospital Medical School,* Miss Margaret D. Snelling (Radiology—Therapy). The following have been recognized as teachers at the Institute of Child Health in the subjects indicated in parentheses: Dr. R. T. Brain (Dermatology), already recognized at the Royal Free Hospital School of Medicine and the Institute of Dermatology; Dr. J. A. Fraser Roberts (Hygiene and Public Health—Medical Genetics), already recognized at the London School of Hygiene and Tropical Medicine.

UNIVERSITY OF BIRMINGHAM

Professors J. M. Smellie and F. A. R. Stammers and Emeritus Professor W. H. Wynn have been appointed representatives of the University on the standing joint committee of the University, the United Birmingham Hospitals, and the Birmingham Regional Hospital Board for the year April 1, 1952, to March 31, 1953, in addition to the Dean of the Faculty of Medicine, Professor A. P. Thomson.

The title of Reader in Endocrinology has been conferred on Dr. P. L. Krohn, Lecturer in Anatomy.

A proposal by the Medical Research Council to institute in the University a unit for research on the experimental pathology of the skin, with Professor J. R. Squire as honorary director, has been approved.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examination indicated:

D.T.M. AND H.—S. K. Dutt, T. H. F. Gillespie, J. J. G. Hanratty, S. S. Izzi, W. G. H. Leslie, D. R. Pershad, S. Poshakrishna, D. H. H. Robertson, Dorothy M. Roels (recommended for Warrington Yorke Medal in Tropical Hygiene), T. Sanderson (recommended for Milne Medal in Tropical Medicine).

UNIVERSITY OF LEEDS

At a meeting of the Court of the University held on May 21 it was decided to confer on July 9 the honorary degree of LL.D. on Professor Albert H. Aldridge, chief surgeon to the Women's Hospital, New York, and clinical professor in obstetrics and gynaecology at Columbia University, New York; on Professor M. A. Bouwdijk Bastiaanse, professor and head of the department of obstetrics and gynaecology in the University of Amsterdam; and on Sir Eardley Holland, President of the Royal College of Obstetricians and Gynaecologists from 1943 to 1946, on the occasion of the thirteenth British Congress of Obstetrics and Gynaecology at Leeds.

At a meeting of the Council of the University on May 21 the receipt was reported of a donation of £500 a year for two years from the British Empire Cancer Campaign (Yorkshire Council) for a fellowship in chemistry, to be named "The J. W. Wootton Fellowship," in recognition of Mr. Wootton's long and valuable service to the cancer campaign.

Cyril Leslie Oakley, M.D., has been appointed to the Brotherton chair of bacteriology. Professor Oakley was educated at Westminster City School and at Chelsea Polytechnic and later at University College, London, and at University College Hospital. He graduated M.B., B.S. from the University of London in 1930, taking the B.Sc., with first-class honours in zoology, in the same year. He proceeded M.D. in 1933. Since 1947 he has been head of the department of immunological and experimental pathology at the Wellcome Research Laboratories, Beckenham, Kent.

Miss Ursula M. Lister has been appointed senior lecturer in obstetrics and gynaecology, and Dr. J. O. Laws Louisa and Elizabeth Ward fellow for two years in the first instance from October 1.

The sum of £1,930 has been subscribed by friends of Emeritus Professor Matthew John Stewart. The Stewart retirement committee proposes (*a*) to present a portrait of Professor Stewart in the form of a bronze plaque to the University, to be placed in the entrance of the Algernon Firth Institute, at an estimated cost of £500; and (*b*) to endow, with the remainder of the money, a Matthew Stewart lectureship, to be delivered every third year by some distinguished pathologist, who would receive a fee of approximately £50. It is suggested that any interest accruing might be used to defray in part or in whole the expenses of a lecturer from abroad who might be invited.

UNIVERSITY OF SHEFFIELD

The following appointments are announced: *Full-time Tutor in Surgery and Lecturer in General Surgery to Dental Students,* P. A. King, M.B., Ch.B. *Full-time Research Assistant in Medicine,* John Mackinnon, M.B., Ch.B., M.R.C.P. *Full-time Demonstrator in Anatomy,* R. M. H. McMinn, M.B., Ch.B. *Part-time Lecturer in Diseases of the Ear, Nose, and Throat,* J. Duncan Gray, M.B., Ch.B., F.R.C.S. *Part-time Lecturer and Clinical Teacher in Medicine,* J. W. Brown, M.D., F.R.C.P.

Mr. D. H. Randall has resigned from the post of Tutor in Surgery on appointment as First Surgical Assistant at St. George's Hospital, London.

The J. G. Graves Medical Research Fellowship has been awarded to Dr. P. G. Walker.

Vital Statistics

Poliomyelitis

Notifications (uncorrected) of acute poliomyelitis in England and Wales are running at a relatively high level for the time of year, though they are still few in number and dispersed throughout the country. In the week ending May 17 (No. 20) the number (37) was the highest ever recorded for that week. The corresponding figure in 1951 was 24 and in 1950 25. In the week ending May 24 (No. 21) this year there were again 37 cases notified. The only higher figure recorded in this week was in 1950, when there were 50. Last year there were 30. The present figures do not necessarily presage a serious outbreak in the summer. An account of recent poliomyelitis epidemics was given by W. J. Martin in the *British Journal of Social Medicine,* 1951, **5**, 236.

Health of Eire

The report of the Department of Health for 1950–1 shows a steady improvement in the health of the people in recent years. The death rate from tuberculosis in 1950 was 78 per 100,000 of the population and was the lowest rate ever recorded in Eire, although this rate is high compared with 36 in England and Wales, 48 in Northern Ireland, and 54 in Scotland. The most important causes of death, in order,

were heart diseases, senility, cancer, and intracranial lesions of vascular origin. International comparison is not valid, since a large proportion of the deaths are uncertified. The percentage of the total deaths uncertified was 12.4 for the country as a whole, but in the west and north-west the proportion was particularly high; in Leitrim County it was 35%. Deaths from senility formed 14% of the total in Eire, compared with 3% in England and Wales. It is obvious from the distribution of the deaths that the mortality from cancer is understated in the older ages and in the areas where the percentage of uncertified deaths is high. The most important causes of infant deaths, in order, were premature birth, diarrhoea and enteritis, pneumonia, and congenital malformations.

1951 Statistics

According to the *Quarterly Return* for the December quarter, 1951, the birth rate during the quarter was 18.7 per 1,000 of the population and was the lowest rate for any quarter during recent years. The infant mortality rate was 41 per 1,000 registered births, being the same as the rate for the fourth quarter of 1950. The general death rate was 10.7 per 1,000, being 1.5 below the rate for the preceding December quarter. The death rate from respiratory tuberculosis was 0.5 per 1,000 and that from other forms of tuberculosis was 0.1; these rates were the same as those of the fourth quarter of 1950.

For the whole year the birth rate was 21.2 per 1,000; this rate was the lowest since 1941. The infant mortality rate was 45 per 1,000 live births, being the same as that for 1950, the lowest recorded rate. The general death rate was 14.3 per 1,000, and was 1.6 above the rate for the preceding year. 1,669 deaths were attributed to tuberculosis of the respiratory system and 438 to all other forms of tuberculosis; these were 191 and 55, respectively, fewer than in 1950.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in April was 128, compared with 132 in the previous month and 124 (revised figure) for April, 1951.

Cases of industrial disease reported during the month were as follows: lead poisoning 6, other poisoning 3, anthrax 2, epitheliomatous ulceration 14, chrome ulceration 39 (manufacture of bichromates 14, chromium plating 8); total 64. There were no deaths.—*Ministry of Labour Gazette*, May, 1952.

Week Ending May 24

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 970, whooping-cough 2,781, diphtheria 25, measles 6,242, acute pneumonia 429, acute poliomyelitis 37, dysentery 269, paratyphoid fever 53, and typhoid fever 1.

Infectious Diseases

During the week ending May 17, in England and Wales, an increase was recorded in the number of notifications of measles 1,255 and scarlet fever 55, and a fall was reported for whooping-cough 88 and dysentery 39.

The incidence of measles rose throughout the country. The largest rises were Norfolk 203, Yorkshire West Riding 182, and Lancashire 100. Only small variations occurred in the returns of scarlet fever. The largest fluctuations in the local trends of whooping-cough were decreases in Warwickshire 45 and Essex 39. With an increase of 11, the notifications of diphtheria reverted to their previous level. The chief features of the returns of diphtheria were an increase of 4 in Yorkshire West Riding and an increase of 3 in London.

The number of notifications of paratyphoid fever were 17 more than in the preceding week, because of outbreaks in Wales. The outbreaks were centred in Glamorganshire 9 (Gelligaer U.D.8) and Monmouthshire 5 (Bedwellty U.D. 4).

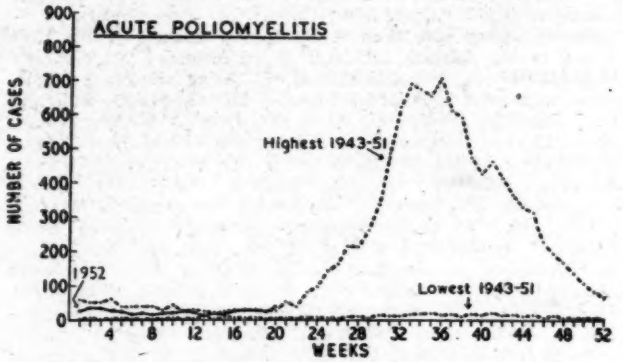
The number of notifications of acute poliomyelitis were 10 more for paralytic cases and 6 more for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 8 (Leeds C.B. 2), Lancashire 4 (Manchester C.B. 2), Devonshire 3 (Plymouth C.B. 2).

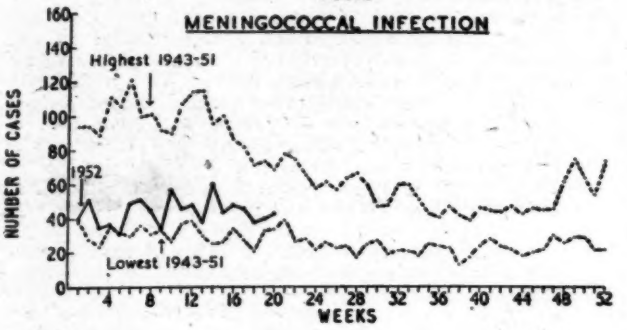
The largest returns for dysentery were Lancashire 132 (Manchester C.B. 37, Liverpool C.B. 22, Oldham C.B. 13, Clitheroe R.D. 11), London 41 (Wandsworth 15, Islington 11), Yorkshire West Riding 21 (Huddersfield C.B. 16), Surrey 18 (Egham U.D. 14), Middlesex 18, Berkshire 18.

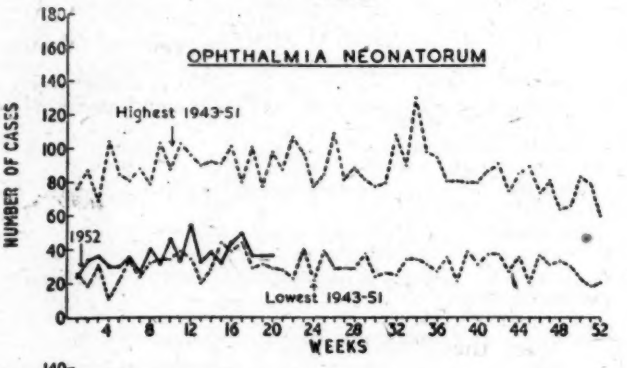
An outbreak of food-poisoning involving 52 persons was notified in Cambridge M.B.

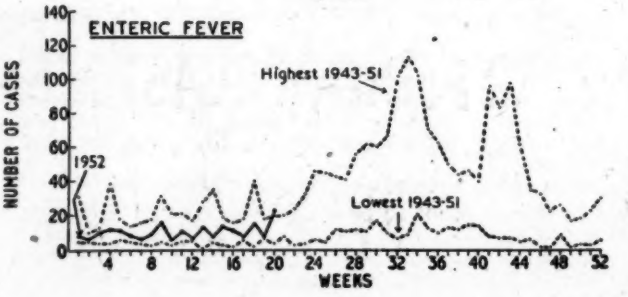
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus - - - - - - -, the figures for 1952 thus ———. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending May 17 (No. 20) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	27	6	10	0	1	31	2	14	1	1
Dysentery	328	41	81	2	2	661	142	109	7	3
Encephalitis, acute	4	0	0	0		5	0	0	0	
Enteric fever: Typhoid	1	0	0	0	1	6	0	2	0	2
Paratyphoid	22	0	1(A)	0		10	0	1(B)	0	
Food-poisoning	134	17		1		62	6		4	
Infective enteritis or diarrhoea under 2 years				14	25				12	24
Measles*	5.749	320	470	237	404	18,381	701	453	240	181
Meningococcal infection	43	2	12	2	1	36	5	22	0	
Ophthalmia neonatorum	36	9	9	0		29	0	13	0	
Pneumonia†	432	36	208	5	4	483	30	212	15	6
Poliomyelitis, acute: Paralytic	25	0	2	2	1	14	2	2	1	2
Non-paralytic	12	1				10	0			
Puerperal fever‡	245	36	23	2		75	12	9	3	
Scarlet fever	1,088	65	183	15	36	991	73	125	18	69
Tuberculosis: Respiratory			151	31				173	30	
Non-respiratory			23	4				33	7	
Whooping-cough	2,905	155	176	102	69	2,556	122	425	59	42

DEATHS in Great Towns	1952					1951				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0		0	0	*1*	0	*0*	0	0
Dysentery	0	0		0			0		1	
Encephalitis, acute		0			0		0			0
Enteric fever	1	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	*5*		2	1	2	*8*		*0*	1	2
Influenza	7	2	1	0	1	*8*	0	*0*	0	2
Measles		0		0	3		0	*2*	0	0
Meningococcal infection		1					1	*0*		
Pneumonia	195	30		7	12	*157*	21		9	11
Poliomyelitis, acute	1	1			0	*1*	0			0
Scarlet fever		1		0	0		0	*0*	0	0
Tuberculosis: Respiratory	141	21	15	5	8	*131*	17	*18*	5	12
Non-respiratory		2	3	0	3		3	*0*	1	6
Whooping-cough	4	0		0	0	*5*	0	*3*	0	1
Deaths 0–1 year	211	20	28	3	13	*237*	35	*34*	7	26
Deaths (excluding stillbirths)	4,926	695	550	99	196	*4,502*	688	*596*	124	195
LIVE BIRTHS	8,228	1277	953	249	424	*7,674*	1282	*1009*	264	358
STILLBIRTHS	172	21	18			*182*	14	*23*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Medical News

Inviting Russian Doctors.—At the Council meeting on May 21 Dr. Rowland Hill presented a report of the International Relations Committee stating that it had been decided to invite six Russian doctors to this country on a friendly visit. This was a result of the recent correspondence in the *Journal*. Dr. Hill said that on the advice of the Foreign Office an approach would be made through the Soviet Embassy in London to the President of the Academy of Sciences of the U.S.S.R.

Durham Medical Gazette.—The *University of Durham Medical Gazette* is hoping to start a postgraduate section. The editor would like to receive short communications (400–800 words) on subjects of general interest such as case-histories from hospital or general practice, original work upon which postgraduates are engaged, or special places and positions in which they find themselves. Particularly welcome will be short items of personal news, successes, etc. Contributions should be sent to the editor, *University of Durham Medical Gazette*, The Medical School, Queen Victoria Road, Newcastle-upon-Tyne.

Presentation to Lord Boyd-Orr.—Lord Boyd-Orr was presented by Lord Haden-Guest on May 19, in the House of Lords, with a specially bound presentation copy of the book *Four Thousand Million Mouths* (12s. 6d. net, Oxford University Press), which was reviewed in the *Journal* of April 19. Edited by Mr. F. Le Gros Clark and Mr. N. W. Pirie, F.R.S., the book is made up of essays by experts on various aspects of food and food production. It has been published in honour of Lord Boyd-Orr on the occasion of his seventieth birthday. Lord Haden-Guest, in a few words of warm welcome, recalled how he had met Lord Boyd-Orr first in the Rowett Institute in Aberdeen, and later at meetings of the Food and Agriculture Organization. In acknowledging the gift, Lord Boyd-Orr made an urgent plea for action. "The first task to be undertaken is the increase of the world food supply. Two out of three people in the world are inadequately fed, and with the rapidly rising tide of population and the falling reserve of food resources the position will get worse unless more vigorous action is taken on a world scale."

Nursing Fellowship at Edinburgh.—A Boots Research Fellowship in Nursing has been founded in the University of Edinburgh, sponsored by Messrs. Boots Pure Drug Company. This research fellowship is attached to the Department of Social Medicine and an advisory group of Faculty members has been appointed to choose the holder. A list is being made of problems that might profitably be investigated.

Guide to Medical Films in Britain.—A revised edition of the catalogue of medical films published in 1948 for the Royal Society of Medicine and Scientific Film Association is just out (*S.F.A. Catalogue of Medical Films*, Harvey and Blythe, price 15s.). It lists over 1,000 films of medical interest available for borrowing, or in some cases purchase, with details of length, colour, medical adviser, etc., and a short synopsis of the contents of each, often with a brief indication of its limitations. This is a thoroughly useful book, which should be available to everyone who uses medical films in teaching or for first-aid demonstrations, or who has to plan an occasional film show.

Hunterian Society's Essay.—The 1951 Gold Medal of the Hunterian Society has been awarded to Dr. G. M. Temple Tate, of Mansfield, Nottinghamshire, and a *proxime accessit* award has been made to Dr. M. Solomon, of Liverpool.

Foreign Decorations.—The Queen of the Netherlands has appointed Professor John Beattie, Dr. J. F. Loutit, and Dr. H. M. Sinclair as Officers of the Order of Orange Nassau, in recognition of services rendered during the war.

NEW ISSUES

British Journal of Ophthalmology.—The next issue of this journal (Vol. 36, No. 6) will be available in a week's time. The principal contents include :

RETROLENTAL FIBROPLASIA. EARLY DEVELOPMENT AND THE EFFECT OF A.C.T.H. IN TREATMENT. C. A. Brown and Beryl Corner.

MECHANISM OF RETROLENTAL FIBROPLASIA. Kazimierz Rubinstein.

COMPARATIVE VALUE OF RADIUM AND DEEP *X* RAYS IN THE TREATMENT OF RETINOBLASTOMA. H. B. Stallard.

CASE NOTES:

OCULAR PATHOLOGY IN A CASE OF XANTHOMATOUS BILIARY CIRRHOSIS WITH INTRAOCULAR INVOLVEMENT. Nancy Lewis.

LEPTOTRICHOSIS CONJUNCTIVAE. Frederick Ridley and Charles Smith.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; obtainable from Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

French Summer Schools in Biochemical Research Techniques.—The Centre National de Coordination des Etudes et Recherches sur la Nutrition et l'Alimentation is organizing this summer three summer schools as follows:

(1) *Paper partition chromatography of amino-acids and peptides. Paper electrophoresis of proteins:* course to be held from September 15 to 29 at the Laboratoire de Chimie Biologique de la Faculté de Médecine de Lille, and at Professor Macheboeuf's department at the Pasteur Institute, Paris. Attendance limited to six persons.

(2) *Methods for the microbiological assay of certain vitamins:* course to be held in Paris from September 29 to October 6 in the following laboratories: Laboratoire de Biochimie de la Nutrition du C.N.R.S., at Bellevue, Directeur: M. Jacquot. Laboratoire de Chimie Médicale de la Faculté de Médecine de Paris, Professor: M. Polonovski. Laboratoire de Microbiologie de l'Inspection Technique des Subsistances de l'Armée, 6 Boulevard des Invalides, Paris. Chef de Travaux: M. Houzé, Vétérinaire-Commandant. Attendance limited to six persons.

(3) *Lactic bacteria of milk and milk products*: course to be held from October 13 to 25 at the Laboratoire de Microbiologie et de Recherches Laitières de l'Institut National Agronomique. Attendance limited to twelve persons.

Both theoretical and practical instruction will be given. No fees will be charged, but those taking part will have to bear the cost of their board and lodging. Applications must be submitted before June 15 to Monsieur le Professeur Terroine, Directeur du Centre National de Coordination des Etudes et Recherches sur la Nutrition et l'Alimentation, 71, Boulevard Péreire, Paris, 17e. The programme of the courses and further details can be obtained from Scientific Office, French Embassy, 22, Wilton Crescent, London, S.W.1.

Nobel Prize Winners Convention.—The second convention of Nobel Prize Winners will take place in Lindau, Lake Constance, from June 23 to 27. Aiming to advance general interest in science, the convention is open to all medical men and their wives and the accent is on popular science rather than a highly specialized level. This year the speakers are winners of Nobel prizes for chemistry. Full details may be obtained from Dr. F. K. Hein, Lindau (B), Fischergasse, 37, Switzerland.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 9

EDINBURGH UNIVERSITY, University New Buildings, Teviot Place.—At Physiology Class Room, 5 p.m., "*Social Medicine and Modern Trends*," lecture-demonstration by Dr. Douglas Guthrie.

INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—5 p.m., "*Infant Mortality*," by Professor A. Sundal (Bergen).

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—5.30 p.m., lecture-demonstration for postgraduates by Dr. Denis Hill.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5 p.m., "*Diabetes and the Eye*," by Dr. T. H. Whittington.

Tuesday, June 10

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Skin Changes in Relation to Endocrine Disturbances*," by Dr. P. M. F. Bishop.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields.—5 p.m., "*Congenital Defects of the Anterior Abdominal Wall*," Arris and Gale Lecture by Mr. G. McC. Wyburn.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5 p.m., "*Bacteriology of the Eye*," by Dr. A. C. Cunliffe.

●SOCIETY FOR THE STUDY OF ADDICTION.—At Meyerstein Lecture Theatre, Westminster Medical School, Horseferry Road, London, S.W., 8 p.m., "*The Activities of the World Health Organization in Drug Addiction*" (Illustrated by Cinematographic Film on Chronic Barbiturism), 4th Kelynack Memorial Lecture by Dr. P. O. Wolff.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, London, W.—5 p.m., "*Antibiotic Synergism and Antagonism*," by Dr. E. Jawetz (California).

Wednesday, June 11

NATIONAL HEART HOSPITAL.—At Barnes Hall, Royal Society of Medicine, 1, Wimpole Street, London, W., 5 p.m., "*Oesophageal Contraction and Cardiac Pain*," St. Cyres Lecture by Dr. William Evans.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.45 a.m., medical clinical-pathological conference; 2 p.m., "*The Nine Human Blood Group Systems*," by Dr. R. R. Race.

ROYAL SANITARY INSTITUTE, 90, Buckingham Palace Road, London, S.W.—2.30 p.m., "*The Incidence of Mycobacterium Tuberculosis in Various Types of Raw and Heated Milk, with Observations on the Control of the HTST Process*," by J. G. Davis, Ph.D., F.R.I.C.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHONETICS, Gower Street, W.C.—At Wellcome Research Institution, Euston Road, N.W., 5.30 p.m., "*A New Sign Language*," demonstration and film, devised by Sir Richard Paget, Bt.

Thursday, June 12

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Central Middlesex Hospital, Park Royal, London, N.W., 8 p.m., general meeting; 8.15 p.m., symposium: "*The Maternity Services*," by Mr. J. S. MacVine, Dr. K. C. S. Skene, and Dr. Dorothy Taylor.

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—4 p.m., "*Pneumonia*," by Professor John Crofton.

ST. ANDREWS UNIVERSITY.—At Materia Medica Department, Medical School, Small's Wynd, Dundee, 5 p.m., "*Brain-stem Mechanisms and their Influence on Survival in Diseases of the Brain*," by Sir Geoffrey Jefferson, F.R.S.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—5 p.m., lecture-demonstration in neurology by Dr. J. H. Paterson.

Friday, June 13

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., "*Congenital and Late Developmental Abnormalities*," demonstration by Dr. H. J. Wallace.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—11.15 a.m., surgical clinical-pathological conference; 2 p.m., "*Experiences with Surgery of the Patent Ductus*," by Mr. O. S. Tubbs.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION: RESEARCH AND CLINICAL SECTION.—At New Theatre, London School of Economics, Houghton Street, Aldwych, W.C., 8 p.m., joint meeting with British Sociological Association. Papers: "*The Sociological Aspects of Suicide*," by Professor M. Ginsberg; "*Researches into Suicide in the London Boroughs*," by Dr. P. Sainsbury. Discussion to be opened by Dr. E. Stengel.

Saturday, June 14

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Eversfield Chest Hospital, St. Leonards-on-Sea, Sussex, 10.30 for 11 a.m., general meeting. "*The Catarrhal Child*," by Dr. E. A. Wood. Mr. A. McArthur will present three cases.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Ansell.—On May 22, 1952, at Liverpool Maternity Hospital, to Betty, wife of Isaac Ansell, M.D., M.R.C.P., a daughter.

Peach.—On May 21, 1952, at Colchester Maternity Hospital, to Pauline, wife of A. N. H. Peach, M.B., F.R.C.S., a brother for Caroline—Michael Hamilton.

Roberts.—On May 26, 1952, at the Churchill Hospital, Oxford, to Betsy (formerly Radovitch), wife of Dr. David St. Clair Roberts, a daughter.

Wilkinson.—On May 22, 1952, at Stanborough's Hydro, Garston, Watford, Herts, to Kathleen, wife of Dr. R. H. Wilkinson, of King's Langley, a sister for Andrew—Julia Mary.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Normal Temperature

Q.—*In what percentage of cases is a "normal" oral temperature of 99° F. (37.2° C.) found?*

A.—The percentage of normal individuals with a mouth temperature of 99° F. or more will depend on the time of day at which the reading is made. The diurnal variation of temperature amounts to at least 1° F. (0.6° C.), so readings between 97° and 99° F. (36.1° and 37.2° C.) can be considered to be quite normal. If the mouth temperature is measured in the late afternoon, when the peak is reached, the proportion of individuals with temperatures of 99° F. will be high, and may amount to 50% of the normal population.

Artificial Insemination (Donor)

Q.—*Are there any special clinics in this country where artificial insemination is carried out? What percentage of success does this procedure carry, assuming the woman is normal? Is it preferable to adopting a child in cases where the husband is sterile but the wife is healthy and both are in agreement with the procedure? Are there any legal hazards involved?*

A.—It is assumed that this question concerns artificial insemination with donated semen (A.I.D.) and not with semen from the husband (A.I.H.). This procedure has been the subject of a leading article, and of a question and answer, in the *British Medical Journal* (1947, **1**, 605 and 625). There has also been an annotation (ibid., 1948, 2, 523) dealing more particularly with the report of the commission on artificial insemination set up by the Archbishop of Canterbury. These should be consulted, as should an article by Mary Barton, K. Walker, and B. P. Wiesner (ibid., 1945, **1**, 40), and one on the legal aspects of A.I.D. by the Rt. Hon. Henry Willink in the *Practitioner* (1947, **158**, 349). The situation has not changed materially in the last four years.

So far as the writer knows there are no clinics sponsored by an official body in which A.I.D. is undertaken. When it is practised it is done under conditions which guarantee secrecy. If the woman is normal and below the age of 40 years, and if the donor is of proved fertility, the procedure is almost certain to result in conception, provided it is carried out at the time of ovulation during several consecutive cycles.

There are religious and ethical as well as legal objections to A.I.D. The legal position remains uncertain, because, although the procedure has been mentioned in Parliament (*British Medical Journal*, 1945, **1**, 614), it has not been the subject of any Act, nor have its possible repercussions been settled by a court judgment in this country. There seems little doubt, however, that any child resulting from A.I.D. is illegitimate; that its registration under the husband's name is illegal; and that it is not entitled to the rights of inheritance. Some authorities take the view that a court of law would regard the act of A.I.D. as one of adultery on the part of the woman and, if the donor is married, on his part too. Also the donor might be liable for maintenance of the offspring. Any doctor contemplating carrying out A.I.D. for one of his patients would be wise to consult his medical defence society first.

It is probably fair to say that most members of the medical profession—including many of those who have the most experience of the problems of infertile marriage—take the view that, irrespective of the legal considerations, A.I.D. is unethical and is rarely in the interests of the patients. Even when the case is carefully chosen on the grounds that both husband and wife are well aware of all the implications and are still anxious for A.I.D., and even when they both appear well satisfied when a conception results, the ultimate outcome can be unsatisfactory. Couples cannot anticipate what their reactions will be a few years later; when a husband asks for his wife to be inseminated he usually has no idea of what it means to have his wife's child by another man in the home. Few doctors feel confident they can choose a case in which A.I.D. is going to convert a childless marriage into a happy one.

The question of adopting a child is not one on which the medical attendant should give advice, although he should point out the advantages and disadvantages. The decision is one for each couple to decide for themselves. If it will satisfy parental desires, adoption obviously involves fewer risks and difficulties than does A.I.D.

Recurrent Styes

Q.—*Is there any effective way of preventing recurrent styes in children? Golden eye ointment, penicillin, and hot fomentations have failed to deal with this problem.*

A.—The underlying cause of recurrent styes is generally a poor state of health, so that general measures are essential in the treatment of this condition. It is advisable to avoid golden eye ointment and fomentations, as these obsolete procedures have a tendency to spread the infection along the lid margin. Penicillin ointment is invaluable in the acute stage, but will do nothing to prevent recurrences. Amongst the general measures, attention to the diet is important. A holiday under open conditions is generally useful.

Coitus during Pregnancy

Q.—*Where can I find information on whether coitus should be discontinued during pregnancy or not?*

A.—On p. 158 of the book "*Any Questions?*" The book can be obtained for 7s. 6d. (postage 6d.) from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

Practical Air Hygiene

Q.—*What is the best way of reducing the bacterial and viral content of the air of places such as operating-theatres, doctors' waiting-rooms, and school classrooms? Is there any evidence that a reduction in the number of pathogenic micro-organisms in the air is accompanied by a reduced incidence of infection?*

A.—In general, a reduction in the microbial content of the air can be achieved by increasing the amount of natural or artificial ventilation, or by the use of aerial disinfectants. No method is "best" for all situations, and a full discussion of the advantages and disadvantages of the various methods would take up much space.

In most circumstances, the air in operating-theatres is probably best kept free from bacteria by ventilation with sterile filtered air supplied under a slight positive pressure (and at the proper temperature and humidity). If possible the air should be led into the room at the ceiling, over the operating-table, and led out at floor level; it will then tend to flush from the working area any bacteria disseminated from bedclothes or dressings. With this ventilation special methods have to be used for dealing with steam from any sterilizers in the theatre.

In doctors' waiting-rooms, schools, offices, and so forth, an increase of natural ventilation is commonly the simplest way of reducing the number of bacteria in the air; it has the disadvantage that it also increases the heat loss and consequently the fuel needed for warming. For this reason vaporization of hexyl resorcinol, or, especially in the United State, triethylene glycol, has been widely advocated, and

both can certainly bring about a reduction in the number of bacteria in the air, as can ultra-violet irradiation of the air in the upper part of the room.

Although there are good general reasons for thinking that a reduction in the microbial content of the air might reduce the incidence of infection, direct evidence of such an effect is extremely scanty. Indeed, it hardly extends beyond the observation of a reduction in streptococcal cross-infection in hospital wards following measures to prevent air-contamination from floors and bedding. At the same time the number of occasions on which the relation has been sought is not great, and adequate methods for the detection of pathogenic bacteria or viruses in the air have been developed only in the last few years. So far only a few large-scale tests of aerial disinfectants and the like have been made, but it must be said that none of those recorded in the literature has shown convincingly that the use of air disinfectants reduced the spread of infection. Air disinfectants should therefore still be regarded as in the experimental stages.

Chemotherapy and Immunity

Q.—*To what extent does the use of sulphonamides and antibiotics prevent children from building up resistance to infection?*

A.—If an infection can be brought to an end by any form of chemotherapy before the body has had time to react to it fully, subsequent immunity will naturally be less than that following an uninterrupted attack. How deficient it will be depends on how early the treatment is given, and on the nature and rapidity of action of the drug used. Sulphonamides act slowly and do not actually kill bacteria; this is left to the normal defences of the body, and consequently the danger of relapse owing to deficient specific resistance after sulphonamide treatment is small. On the other hand, penicillin kills bacteria, and if, for instance, it is given early in scarlet fever, the attack is aborted, and a relapse is liable to occur which may be as severe as the original illness. The remedy in this case is to continue penicillin treatment not only until symptoms and signs have disappeared but until the streptococcus has been eliminated from the throat, which will usually mean six to seven days. The same difficulty has been encountered in the treatment of typhoid fever with chloramphenicol, and here it is wise to anticipate a relapse by giving a second course. In most other infections there is no particular liability to relapse, unless dosage and duration of treatment are inadequate by ordinary standards. There are no good grounds for delaying treatment in any infection in order to allow the body to play its own part in overcoming it.

Amidone

Q.—*Are there any dangers in prolonged treatment with amidone (5 mg. nightly)?*

A.—Prolonged administration of amidone in therapeutic doses is unlikely to be followed by any dangerous organic disorders. It should be remembered, however, that it is a drug of addiction, though in the very small dosage suggested the danger of addiction, even with prolonged treatment, is extremely slight.

Venesection

Q.—*What are the modern indications for venesection? What is a reasonable amount of blood to remove at a single sitting?*

A.—There are two chief indications for venesection: polycythaemia vera and heart failure. In polycythaemia vera repeated venesection is probably as good a way as any of controlling the situation. It is usual to remove half a litre at a sitting, and this may be repeated at weekly intervals until the blood count is around normal, when the intervals between venesection may be increased. Venesection improves all patients with heart failure except those secondary to anaemia, but it is rarely necessary, failure usually responding quickly to rest, digitalis, mercurial diuretics, and a low sodium diet. When failure is extreme, however, and when it does not seem to be responding satisfactorily to the methods mentioned, venesection can be very helpful. By lowering the venous pressure it unloads the failing heart, and so improves the circulation. It should not, as a rule, be repeated. The usual amount taken off is about half a litre. Venesection may also be used in acute pulmonary oedema which does not respond to posture, venous ligatures on the thighs, morphine, aminophylline, and oxygen.

Therapeutic Abortion in Acute Heart Failure

Q.—*What is the best way of inducing a therapeutic abortion in a patient with acute heart failure?*

A.—This problem should not arise, because abortion should not be induced in the presence of acute heart failure. Treatment should be directed to the heart condition, and only when compensation is restored is it justifiable to consider terminating the pregnancy. The method then to be adopted depends on the circumstances of the particular case, and these include the duration of the pregnancy, the parity of the patient, and the state of the cervix. If the pregnancy is advanced more than 12 weeks abdominal hysterotomy under local analgesia is often the method of choice.

NOTES AND COMMENTS

Quaternary Ammonium Antiseptics.—Dr. H. B. MAY (London) writes: The author of the answer to the query ("Any Questions?" May 3, p. 985) does less than justice to some of the large number of quaternary ammonium compounds. The efficiency of some of these substances—e.g., benzalkonium chloride against *Ps. pyocyanea* both in test-tube experiments and on infected skin is equal to that of many widely used antiseptics of the chlor-xylenol type. It is well-known that cetrimide of commercial purity has very little action on *Ps. pyocyanea*, but it must not be implied that all quaternary ammonium compounds have a similar disadvantage. In an experiment designed to test the relative efficiency of a number of disinfectants on human skin an area of the forearm was heavily contaminated with *Ps. pyocyanea* and different areas were wiped with solutions of benzalkonium chloride (0.1 w/v) and a corresponding bromide (0.1% w/v). On subsequent subculture at the end of one minute, both areas of skin showed no growth, while a control area wiped with saline gave a confluent growth of the contaminating organism.

Redheads.—Dr. G. FIELDING (Leicester) writes: It is news to me that Jews belong to the dark races ("Any Questions?" May 24, p. 1143), as their two main types in Europe belong either to the Eastern European group (Ashkenazi) or the Spanish–Dutch group (Sephardi), neither of whom can be called dark. The Sephardi are often very fair, as also are Jews born in Israel. Red-haired Jews are very common.

Correction.—We must apologize to Dr. J. H. Kellgren for an error in his qualifications at the head of his Goulstonian Lectures which were published in our issues of May 24 (p. 1093) and May 31 (p. 1152). Dr. Kellgren is, of course, a Fellow of the Royal College of Physicians of London, *not* a Member as was stated.

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated

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